ELSEVIER
SAUNDERS

CRITICAL CARE CLINICS

theclinics.com

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) xiii–xiv

CRITICAL
CARE
CLINICS

Preface

José R. Maldonano, MD, FAPM, FACFE
Guest Editor

Critical care units are among the most stressful and psychologically challenging places to be in a general medical hospital, whether you are a health care professional or a patient. The purpose of this volume is to help intensivists, anesthesiologists, internists, and surgeons understand the complex and diverse psychologic problems their patients face during their stay in the ICU.

Drs. Arciniegas (of the University of Colorado) and McAllister (of Dartmouth Medical School) discuss the neurology of traumatic brain injury with a special focus on the neurobehavioral sequelae of head trauma, including the evaluation and treatment of behavioral problems following trauma. The United States population is increasingly older. Dr. Lee and his colleagues from Johns Hopkins provide an excellent review of the presentation and management of dementia and cognitive impairments in the critical care units.

Delirium is the most common neurobehavioral disorder experienced by critically ill patients. It affects patient's morbidity and mortality, and it also interferes with the safe delivery of care and affects the outcome of treatment. In two separate articles, Dr. Maldonado (of Stanford University School of Medicine) conducts a comprehensive review of the epidemiology, etiologic factors, characteristics, and methods of diagnosis and summarizes the evidenced-based data on methods of treating and preventing delirium in critical care units. Next, Dr. Maldonado distills years of available research and offers a comprehensive theory for understanding the pathophysiology and neurobiology of delirium. Taken together, these models may help guide future research into effective techniques for preventing and treating delirium.

doi:10.1016/j.ccc.2008.06.003 *criticalcare.theclinics.com*

Drs. Ferrando (of the Weill Medical College of Cornell University) and Freyberg (of Columbia University College of Physicians and Surgeons) review the infectious agents that directly infect the central nervous system and may complicate the assessment and clinical management of ICU patients. They suggest treatments for each disorder covered. Substance abuse and potential withdrawal syndromes are common causes for admission to critical care units and often complicate the management of these patients. In their article, Drs. Tetrault and O'Connor (of the Yale School of Medicine) review the epidemiology of substance abuse and provide clinical recommendations regarding the treatment of common withdrawal syndromes.

Mood disorders and suicide attempts and their sequelae are unfortunate common causes for admission to the ICU. Drs. Steven Dubovsky (of the University of New York at Buffalo) and Amelia Dubovsky (Harvard Medical School) offer an insight into the aftermath of attempted suicide and the acute management of these patients until stabilization and transfer to the appropriate psychiatric facility is made. Similarly, the incidents leading to an admission to an acute care unit and the procedures and process of a critical care unit may render patients and family members liable to suffer a number of anxiety symptoms. Drs. Kross, Gries, and Curtis (of the University of Washington) discuss the presentation and management of posttraumatic stress disorder as a sequela to the critical care environment. Dr. Shapiro and colleagues (of Columbia University) summarize the specific psychiatric challenges that are experienced by patients in acute, intensive, and critical care who have heart and lung disease. They focus on the most common psychiatric presentations of these patients and discuss effective treatment strategies to help optimize care.

Patients undergoing organ transplantation invariably are managed in the critical care setting both before and after transplantation. This population, too, is likely to experience a number of psychiatric complications. In their article Drs. DiMartini and Dew (of the University of Pittsburg), Crone (of George Washington University), and Fireman (Oregon Health and Science University) discuss the pretransplantation psychosocial evaluation and review the psychologic complications commonly seen in patients undergoing transplantation. Finally, during the average critical care unit stay, critically ill patients are exposed to a significant number of medications. Many of these agents are used specifically to affect the patient's cognition and behavior or have psychoactive side effects. Drs. Smith, Wittmann, and Stern (of Massachusetts General Hospital) review the most common medical complications associated with the use of psychoactive agents.

José R. Maldonado, MD
Department of Psychiatry & Behavioral Sciences
Stanford University School of Medicine
401 Quarry Road, Office #2317
Stanford, CA 94305, USA

E-mail address: jrm@stanford.edu

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 635–656

CRITICAL
CARE
CLINICS

Medical Complications of Psychiatric Treatment

Felicia A. Smith, MD[a,b,c,*],
Curtis W. Wittmann, MD[a,d], Theodore A. Stern, MD[a,c]

[a]*Department of Psychiatry, Harvard Medical School, Boston, MA, USA*
[b]*Transplant Psychiatry Service, USA*
[c]*The Avery D. Weisman, MD, Psychiatry Consultation Service, Department of Psychiatry, Massachusetts General Hospital, Warren 605, 55 Fruit Street, Boston, MA 02114, USA*
[d]*Department of Psychiatry, Massachusetts General Hospital, WACC 812, Boston, MA 02114, USA*

Psychiatric medications are frequently an essential component of care for critically ill patients. Their use may lead to medical complications, however, as a result of (1) direct toxicity from psychotropic medications, (2) drug-drug interactions, or (3) intoxication or withdrawal states. These complications may be a nuisance (eg, dry mouth and nausea) or serious and life-threatening (eg, neuroleptic malignant syndrome [NMS] and cardiac arrhythmias). This article addresses the most important medical complications (organized by organ systems) of psychiatric treatment.

Central nervous system

Neuroleptic malignant syndrome

NMS is a serious and rare idiopathic clinical syndrome that is most often manifest by high fever, muscle rigidity, autonomic instability, and altered mental status. It is caused by a decrease in central nervous system dopamine function and is fatal in approximately 10% of cases [1]. Antipsychotics (eg, haloperidol) that are potent dopamine-blockers are generally implicated, although atypical antipsychotics with less dopamine receptor affinity (eg, olanzapine, quetiapine, and risperidone) have also been linked with

* Corresponding author. Department of Psychiatry, Massachusetts General Hospital, Warren 605, 55 Fruit Street, Boston, MA 02114.
E-mail address: fsmith2@partners.org (F.A. Smith).

0749-0704/08/$ - see front matter
doi:10.1016/j.ccc.2008.05.004 *criticalcare.theclinics.com*

NMS [2]. Other dopamine-blocking agents frequently used in the medically ill (including metoclopromide, droperidol, and promethazine) may also cause NMS, as can abrupt withdrawal of dopamine agonists (eg, levodopa or amantadine). The incidence of NMS varies (especially in the setting of disparate diagnostic criteria), but it is approximately 0.2% in those treated with neuroleptics [3]. The fact that NMS is rare should not obscure the importance of early recognition and diagnosis of this syndrome given its potentially fatal course.

Several risk factors predispose one to NMS: dehydration, a history of underlying brain abnormalities, low serum iron levels, and concomitant use of lithium [4]. The syndrome typically develops over several days and lasts approximately 5 to 10 days [5] even after the offending agent has been discontinued (it is longer with depot neuroleptics). Major clinical manifestations include high fever (often $>40^{\circ}C$), so-called "lead-pipe" rigidity, confusion or altered level of consciousness, and autonomic instability. Downstream complications (including renal failure caused by elevated creatine phosphokinase or rhabdomyolosis from muscle breakdown in the setting of rigidity and hyperthermia) may be severe. Respiratory failure, pulmonary embolus, and disseminated intravascular coagulation are also seen. The potential manifestations and complications of NMS are as follows:

Major features
- Severe muscle rigidity
- Fever

Associated features
- Depressed level of consciousness (stupor or coma)
- Autonomic disturbance
- Dysphagia
- Mutism
- Tremor
- Incontinence

Laboratory results
- Leukocytosis
- Elevated creatine phosphokinase
- Low serum iron

Of particular note is that the symptoms of NMS overlap considerably with those of other medical illnesses (eg, central nervous system infection, malignant hyperthermia, and anticholinergic delirium) making it difficult to provide a definitive diagnosis, especially in an ICU setting. When the diagnosis is unclear, the symptoms of NMS should be treated and offending agents discontinued. Care should be provided, at least initially, in an ICU setting, because the complications of the syndrome may be serious. After removing all dopamine-blocking agents, treatment is largely supportive and guided by the particular constellation of symptoms that arise. These include use of antipyretics and cooling blankets for high fevers, rehydration,

and use of standard treatments for autonomic instability. Pharmacotherapy (eg, with dantrolene for muscle rigidity or bromocriptine and amantadine to reinforce the dopamine system) is often used, but it has not been shown to be consistently superior to application of supportive measures [1]. Finally, neuroleptics may be cautiously reintroduced to patients who have recovered from NMS after 2 weeks of abstinence.

Serotonin syndrome

Serotonin syndrome results from serotonergic excess; it is most often described by a triad of mental status changes, abnormal neuromuscular findings, and autonomic hyperactivity [6]. Although there are numerous potentially causative agents (Box 1), antidepressants are most commonly implicated. Signs and symptoms of serotonin syndrome are varied, ranging from mild (with diarrhea and nausea) to life-threatening (eg, with delirium, autonomic instability, and hyperthermia). Box 2 provides a more complete list of the clinical features of serotonin syndrome. The onset is generally quite rapid and risk factors include overdose of a serotonergic agent and polypharmacy (ie, with multiple drugs working on the serotonin system or inhibiting the metabolism of serotonergic drugs). The combinations of medications most strongly associated with severe cases of serotonin syndrome include monoamine oxidase inhibitors (MAOIs) (eg, phenelzine, tranylcypromine, and isocarboxazid) in conjunction with meperidine, dextromethorphan, and selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram) [6]. Concomitant use of illicit drugs (eg, ecstasy and cocaine) is also quite dangerous and should not be overlooked. Because of its protean manifestations, serotonin syndrome is difficult to differentiate from other medical conditions and from NMS (especially when patients are taking both dopamine antagonists and serotonergic drugs). Typically, serotonin syndrome involves hyperarousal or agitation, whereas stupor is most often seen with NMS.

Serotonin syndrome is generally self-limited and quick to resolve; however, it can be fatal. The mainstay of treatment is removal of the precipitating serotonergic agents. Like NMS, supportive care that is tailored to individual manifestations of the syndrome is essential. In particularly severe cases, 5-HT_{2a} antagonists (eg, cyproheptadine) may be used, although their efficacy has not been convincingly established [7]. Benzodiazepines are also often used to help manage agitation. Unfortunately, there are little data to guide rechallenge with serotonergic agents after the onset of serotonin syndrome; at the very least, avoidance of multidrug regimens with significant potential drug-drug interactions seems prudent.

Delirium

Delirium is defined as a disturbance of consciousness that cannot be accounted for by dementia; it involves the reduced ability to focus, to

Box 1. Selected serotonergic medications

Selective serotonin reuptake inhibitors
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline

Atypical antidepressants
Buspirone
Duloxetine
Mirtazapine
Nefazodone
Trazodone
Venlafaxine

Tricyclic antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Nortriptyline

Monamine oxidase inhibitors
Isocarboxazid
Moclobemide
Phenelzine
Selegiline
Tranylcypromine

Stimulants
Amphetamines
Cocaine
MDMA (ecstasy)

Analgesics
Fentanyl
Meperidine
Tramadol

Antimigraine agents
Sumatriptan

Antibiotics
Linezolid

Cold remedies
Dextromethorphan

Data from Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112–20; Fricchione GL, Huffman JC, Stern TA, et al. Catatonia, neuroleptic malignant syndrome, and serotonin syndrome. In: Stern TA, Fricchione GL, Cassem NH, et al, editors. Massachusetts General Hospital handbook of general hospital psychiatry, 5th edition. Philadelphia: Mosby; 2004. p. 513–30.

sustain, or to shift attention and it tends to fluctuate during the course of the day [8]. Delirium is common in the critical care setting given the complicated nature of illnesses treated there, and although a comprehensive discussion of this condition is beyond the scope of this article, a brief outline of delirium as a result of psychiatric treatment is warranted. In this context, an altered mental status most often results from use of, or withdrawal from, particular medications. Typically, these include benzodiazepines (both their use and withdrawal) and anticholinergic agents (often used to facilitate sleep or to ameliorate side effects of other psychotropics, such as antipsychotics). In rare instances both serotonergic agents and antipsychotics may also lead to delirium in the cases of serotonin syndrome and NMS, respectively. Delirium from benzodiazepine (or barbiturate) use is seen more frequently (likely caused by the prevalence of their use in the general hospital setting). Patients become confused and may alternate between being somnolent and agitated. Nystagmus and slurred speech may serve as clinical clues.

Box 2. Clinical features of serotonin syndrome

Neuromuscular excitation
  Clonus
  Hyperreflexia
  Akathisia
Muscular rigidity (variable)
Hyperthermia (variable)
Agitation
Diaphoresis
Mydriasis
Autonomic instability
  Hypertension
  Tachycardia
Increased bowel sounds or diarrhea

Data from Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112–20.

The treatment involves discontinuation of the benzodiazepine and provision of a safe environment until the delirium clears. This is the opposite of the treatment of delirium from benzodiazepine withdrawal, which occurs in the setting of abrupt cessation (or significant reduction of dose) of this class of medication. In addition to delirium, clinical manifestations of benzodiazepine withdrawal (including fever, tachycardia, hypertension, hyperarousal, diaphoresis, tremor, hyperreflexia, hallucinations, and seizures in severe cases) are similar to those of alcohol withdrawal. Treatment includes reinstitution of a benzodiazepine (most are cross-reactive at the γ-aminobutyric acid receptor); titrating the dose to the resolution of symptoms; and then tapering slowly.

Anticholinergic delirium, however, results when high doses or combinations of anticholinergic agents are used. Rudolph and coworkers [9] have developed a risk scale to rate the potential for delirium from anticholinergics typically used in psychiatric and medical settings. The clinical presentation most often seen with this type of toxicity includes agitation; hypervigilance; dry mouth; hot and erythematous skin; constipation; urinary retention; and autonomic instability (involving tachycardia, tachypnea, and hypertension). Treatment involves removal of the precipitating agents and administration of supportive care. Although intravenous physostigmine may be used effectively, conservative management is generally preferred because of potentially serious side effects (eg, seizures) from physostigmine administration. NMS, serotonin syndrome, and delirium from benzodiazepine withdrawal or anticholinergic toxicity are all potentially serious complications of psychiatric treatment encountered in the critical care setting with similar symptoms. Table 1 outlines their characteristic features to help distinguish among them.

Seizures

Some antipsychotics and (to a lesser extent) antidepressants have been implicated in lowering the seizure threshold and causing seizures. The SSRIs seem to have the safest profile in this regard, whereas clomipramine,

Table 1
Distinguishing features of NMS, serotonin syndrome, and anticholinergic delirium

Clinical signs	Neuroleptic malignant syndrome	Serotonin syndrome	Anticholinergic delirium
Hyperthermia	++	+/-	+/-
Rigidity	++	+	-
Reflexes	Decreased	Increased	Normal
Mental status	Stupor/coma	Agitation/coma	Agitation
Skin	Pallor/diaphoresis	Diaphoresis	Hot and dry
Mucosa	Sialorrhea	Sialorrhea	Dry
Bowel sounds	Wnl or hypoactive	Hyperactive	Hypoactive

Data from Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112–20.

chlorpromazine, bupropion, and clozapine seem to be more problematic [10]. General risk factors include a history of seizures; rapid dose escalation; higher doses of medication (including overdose); and a history of head trauma or cerebrovascular accident. In the case of bupropion in particular, seizure risk is associated with higher doses (especially with doses greater than 450 mg/day and with its use in individuals with an eating disorder or a seizure disorder) of the immediate-release preparation. There is less risk at lower doses and with the sustained-release formulation [11]. With regard to antipsychotics, clozapine, olanzapine, and quetiapine are thought to play a more significant role in evoking seizures than are haloperidol and risperidone [12,13]. Withdrawal from benzodiazepines and from barbiturates may also lead to seizures.

Cerebrovascular accidents

Recent data suggest that use of atypical antipsychotics in the elderly with dementia increases the risk of stroke. Specifically, a 2006 meta-analysis of placebo-controlled trials of atypical antipsychotics (olanzapine, risperidone, quetiapine, and aripiprazole) used in patients with dementia [14] indicated a significantly increased risk of cerebrovascular accident in this population and a small increase in mortality [15]. Other studies have looked at similar risks in the elderly who were treated with conventional antipsychotics versus atypicals; mixed results were noted [16–18]. Although more data are needed to clarify this situation, management of agitation and behavioral disturbances in the medically ill elderly with dementia is currently best served by weighing the risks of treatment with the risks of ongoing behavioral disturbance (taking into account alternative treatment strategies and the underlying risk factors for cerebrovascular accident) [19]. Finally, several case reports have suggested an association between serotonergic antidepressants and the so-called "Call-Fleming syndrome" (diffuse cerebral vasoconstriction) leading to stroke [20,21]. Although this comprises merely an association, any patient who presents with the hallmark symptoms of Call-Fleming (ie, severe headache and focal deficits with evidence of cerebral ischemia or vasoconstriction) merits a thorough review of medications that enhance serotonergic transmission.

Extrapyramidal symptoms

Each of the four main extrapyramidal syndromes (eg, dystonia, akathisia, parkinsonism, and tardive dyskinesia) associated with use of psychotropic medications is seen in the medical setting. Acute dystonia and akathisia (the inability to sit still) are thought of as acute manifestations of extrapyramidal syndromes, whereas parkinsonism and tardive dyskinesia are subacute or chronic forms. Acute dystonia involves contraction of voluntary muscle that leads to a postural distortion. The neck is a common site of dystonia, whereas oculogyric crisis tends to be better known although considerably

less common [19]. Acute dystonia usually appears early in the course of antipsychotic treatment (or of another dopamine blocker) and is more common with higher doses and a younger age [22]. Treatment consists of stopping the offending agent and administering an anticholinergic agent. Akathisia (with restlessness, pacing, or fidgetiness) often is seen when a patient receives an antipsychotic. Patients often describe a subjective sensation of inner restlessness or "crawling out of one's skin." β-Blockers may help reduce this sensation. Higher-potency typical antipsychotics are associated with more extrapyramidal syndromes than are lower-potency agents, whereas the newer atypical antipsychotics seem to confer even less risk [5,23].

The more chronic forms of extrapyramidal syndromes (including parkinsonism and tardive dyskinesia) are also caused by antipsychotics and by other dopamine-blockers (eg, phenothiazine antiemetics or metoclopramide). Parkinsonism is generally subacute (ie, arising weeks to months after a dopamine blocker is started), and includes a triad of bradykinesia, rigidity, and tremor that mimics the disease by the same name. Of the antipsychotics, the atypical agents, quetiapine and clozapine, least commonly cause parkinsonian side effects. If the offending agent cannot be stopped, an anticholinergic agent can be added to ameliorate these symptoms. Finally, tardive dyskinesia is generally the most chronic form of extrapyramidal syndromes, starting months or years after treatment with an antipsychotic. It generally starts with involuntary movements of the muscles of the tongue, lips, mouth, and face [19], although any part of the body may be affected. Dyskinesias generally worsen with continued antipsychotic use, and the elderly are at greater risk of developing tardive dyskinesia. For patients who require ongoing antipsychotic treatment, a switch to clozapine or quetiapine often leads to improvement in symptoms [24].

Sedation

Sedation is a side effect of many psychotropics (eg, most antipsychotics, anticonvulsants, mood-stabilizers, benzodiazepines, and certain antidepressants). Unfortunately, oversedation predisposes patients to medical complications (eg, aspiration, deep venous thrombosis [from an inability to mobilize], malnutrition, and general deconditioning). This is especially true when these medications are added to already complex regimens that may include other sedating agents (eg, narcotics), or when the underlying illness predisposes the patient to somnolence (eg, a central nervous system infection or a respiratory infection). Although psychotropics are often important adjuncts or essential components of treatment, the motto, "start low, go slow" provides a framework for dose titration in critical care settings.

Thermoregulation

Antipsychotics can also interfere with temperature regulation, making those who take them poikilothermic and susceptible to both hyperthermia

and hypothermia [25]. This is especially true when antipsychotics are-combined with anticholinergic agents. Medically ill patients may be even more susceptible to these effects given comorbid conditions that also affect temperature regulation.

Cardiovascular

Psychotropics contribute to a variety of cardiovascular effects, including arrhythmias and conduction disturbances; changes in blood pressure (hypotension and hypertension); and in rare cases, myocardial infarction and myocarditis.

Arrhythmias

Tricyclic antidepressants (TCAs) have quinidine-like effects on cardiac conduction, leading to delays in cardiac conduction, increases in heart rate, and prolongation of the QT and PR intervals. Although these effects are often insignificant in patients without underlying cardiac conditions, they may become meaningful in those who are predisposed to arrhythmias. When administered to patients with hypomagnesemia, hypokalemia, or concurrent QTc prolongation, TCAs may cause a life-threatening depression of cardiac conduction, heart block, or ventricular dysrhythmias. This is especially true when TCAs are coadministered with other class I antiarrhythmics (eg, quinidine and procainamide). Furthermore, when given to patients with atrial fibrillation, quinidine-like drugs (eg, TCAs) may lead to ventricular dysrhythmias; extreme caution is advised [5].

Although all antipsychotics can affect electrocardiographic intervals, those agents with the greatest propensity to prolong the QTc are thioridazine, pimozide, droperidol, sertindole, mesoridazine, and ziprasidone. The atypical antipsychotics and haloperidol are generally thought to be safest in this regard, although it is important to note that there are no head-to-head studies to confirm this. Risk factors for QTc prolongation with antipsychotics are the same as those for TCAs. In addition, concomitant use of other medications that either increase levels of antipsychotics or TCAs by cytochrome P-450 interactions (eg, fluoxetine and paroxetine), or prolong the QTc themselves (eg, fluoroquinolones and methadone) increase the risk of this complication by their additive effects. Checking an EKG and maintaining potassium and magnesium in the high normal ranges is recommended for patients taking antipsychotics and TCAs (because they are at risk for QTc prolongation).

Orthostatic hypotension

Orthostatic hypotension is a common and potentially serious side effect of antipsychotics, TCAs, MAOIs, and the atypical antidepressant, trazodone.

As far as antipsychotics are concerned, the lower-potency agents and atypical antipsychotics seem to be the worst offenders, whereas higher-potency agents (eg, haloperidol) confer less risk. Patients with underlying congestive heart failure or dehydration are particularly susceptible as are those who are receiving vasodilators or α_1-adrenergic blockers. Orthostatic hypotension may lead to significant morbidity, including falls (especially in the elderly) and impaired tissue perfusion.

Hypertension

Hypertension is also a potential side effect of psychotropics, including venlafaxine, bupropion, and stimulants (eg, methylphenidate and amphetamine). Although this is usually relatively mild, blood pressure should be checked in patients receiving these medications at the time of their initiation and with dose increases. A more serious complication is that of hypertensive crisis with MAOIs, where patients experience an abrupt rise in blood pressure, and headache, nausea, vomiting, and diaphoresis. If not treated quickly with an α-blocker (eg, phentolamine or nifedipine), the dread complications of intracranial hemorrhage or myocardial infarction may ensue. Hypertensive crisis in this case is a consequence of the interaction of the MAOI with vasopressor amines, anorexiants, stimulants, pain killers (ie, meperidine), and many over-the-counter cold preparations [26] or ingestion of tyramine-containing food products. Drug-drug interactions should be checked carefully for any patient receiving a MAOI and patients should be placed on a tyramine-free diet.

Myocarditis and cardiomyopathy

Myocarditis and cardiomyopathy have each been linked with use of several psychotropics, although most consistently with clozapine [27]. A recent retrospective review puts the incidence of myocarditis between 0.7% and 1.2% of treated patients [28] with the condition generally developing during the first few weeks of treatment. Cardiomyopathy, however, is thought to result from more chronic use. The pathophysiology may involve a type I IgE hypersensitivity reaction as evidenced in part by peripheral eosinophilia (which is often present) [29]. Clinical features and treatment are similar to those of myocarditis of other etiologies. Stopping clozapine is the first step in treatment of clozapine-associated cardiomyopathy.

Gastrointestinal

Gastrointestinal complications of psychiatric illnesses range from minor discomfort to severe complications (including pancreatitis and acute liver failure). This section addresses the minor complications and then focuses on the more severe complications.

Xerostomia

Xerostomia is one of the most common complications of psychiatric medications. It is most frequently related to treatment with anticholinergics (eg, diphenhydramine and benztropine) and TCAs (eg, amitriptyline, nortriptyline, imipramine, and desipramine). It is also associated with many other commonly used medications, including the SSRIs and some antipsychotics with significant anticholinergic properties (eg, chlorpromazine, thioridazine, olanzapine, and quetiapine). Xerostomia has been associated with dental caries, but with short-term use it is primarily a source of patient discomfort.

Sialorrhea

Excessive salivation has also been associated with use of psychotropics, most notably with the antipsychotic clozapine; roughly 31% of clozapine users are affected [30]. It has also been associated with use of risperidone; 1% to 6% of adults and up to 22% of children receiving risperidone has experienced this side effect [31]. Among clozapine users, sialorrhea may result from muscarinic stimulation or from α_2 antagonism [32]. Although a nuisance during the day, it has been linked to aspiration pneumonia during sleep. Several interventions have been used, but the use of ipratropium nasal inhalers has been most efficacious.

Gastrointestinal distress

Gastrointestinal distress (nausea, vomiting, and diarrhea) has been widely reported with psychotropics, but it seems to be most common with use of SSRIs (including fluoxetine, duloxetine, venlafaxine, and paroxetine); nausea occurs in 20% to 25%, and vomiting occurs in 2% to 3% of individuals. This adverse effect is most prevalent at the outset of therapy, although it may also be seen in overdose. Although these symptoms are primarily a source of irritation for patients, one must monitor for signs of toxicity. In patients taking lithium, for example, the constellation of nausea, vomiting, and tremor often heralds lithium toxicity. In these cases, a thorough history, physical examination, and laboratory evaluation (eg, checking a lithium level, assessing renal function, and checking serum electrolytes) helps to differentiate between a relatively benign medication side effect and a major complication.

Pancreatitis

Pancreatitis is a rare but serious complication from psychiatric medications that is most commonly associated with use of clozapine, risperidone, olanzapine, and valproate. Valproic acid therapy has been associated with pancreatitis without a clear relation to dose or serum level. Cases have

occurred both early and late in the course of treatment with valproic acid. Atypical antipsychotics have also been associated with pancreatitis. In cases reported to the Food and Drug Administration, 40% were caused by clozapine, 33% by olanzapine, and 16% by risperidone [33]. Twelve percent of the cases were associated with haloperidol, but in 50% of these cases an atypical antipsychotic was also prescribed [33].

Hepatic dysfunction

Hepatic effects of psychotropics are commonly reported and range from elevations in liver function tests and hyperammonemia to hepatitis and acute liver failure. This section focuses on the most severe and most common complications. The agent most often linked with hepatotoxicity is valproic acid. Valproic acid is associated with elevation in liver function tests with both acute and chronic use and monitoring is recommended. Acute liver failure most commonly occurs within the first 6 months of treatment; the risk of fatality is 1 of 37,000 for adults on valproate monotherapy [34]. Hyperammonemic encephalopathy has also been reported with valproic acid during both early and chronic treatment and it can occur without a change in liver function tests. Episodes of confusion in patients taking valproic acid should prompt the clinician to check an ammonia level. If elevated, stopping the medication generally reverses the problem. In mild cases of hyperammonemia (while taking valproic acid), L-carnitine at doses of 50 to 100 mg/kg/d may be used to improve symptoms and to reduce ammonia levels [35].

Hepatic complications (including hepatitis and liver failure) have also occurred with other anticonvulsants (specifically lamotrigine and carbamazepine) that are commonly used for psychiatric indications. Many antidepressants have also been associated with liver abnormalities, but nefazodone more commonly has been associated with fatal liver failure (occurring at a rate of 1 per 250,000–300,000 patient-years) [36]. Finally, hepatic complications have been associated with use of several antipsychotics. Chlorpromazine has been connected to cholestatic jaundice and to hepatocellular jaundice, with an overall rate of 0.1% in all patients [37]. Notably, patients older than 70 years were 12 times as likely to have a hepatic complication caused by chlorpromazine as those under the age of 50, with a risk of 0.3% in those older than 70 years [37].

Immunologic

There are relatively few immunologic complications from psychiatric treatments; however, many medications are associated with drug-induced systemic lupus erythematosus. This section focuses primarily on the medications that have been most frequently associated with this complication and other immunologic issues are briefly discussed.

Drug-induced systemic lupus erythematosus

Some important differences exist between idiopathic systemic lupus erythematosus and drug-induced systemic lupus erythematosus. Drug-induced systemic lupus erythematosus is often associated with polyarthralgias, arthritis, rash, or fever. Renal and central nervous system involvement are rarely seen in drug-induced systemic lupus erythematosus. Anemia, leukopenia, and lymphadenopathy are also less common in drug-induced systemic lupus erythematosus when compared with systemic lupus erythematosus. Carbamazepine has been reported in several case reports as a cause of drug-induced systemic lupus erythematosus [38]. Although drug-induced systemic lupus erythematosus usually occurs early in treatment, it may arise at any point in the course of treatment. Chlorpromazine and other phenothiazines have been associated with positive antinuclear antibodies. This association seems related to the length of therapy and to the dose, with increased rates of antibodies associated with more than 3 years of therapy [39] and with doses greater than 400 mg/day [40]. Most patients remain asymptomatic, but some go on to develop drug-induced systemic lupus erythematosus. Clozapine and lithium have also been reported as a cause of drug-induced systemic lupus erythematosus, although there have only been a few published case reports.

Lymphadenopathy

Lymphadenopathy has also been associated with some psychotropics (including carbamazepine, duloxetine, and in one report with lamotrigine) [41]. Duloxetine has been reported to cause lymphadenopathy, at rates ranging from 0.1% to 1% [42].

Renal

Potential renal complications from psychiatric medications range from an increase in urinary frequency to the development of nephrotic syndrome. Among psychotropics, lithium is one of the most well-known agents with significant renal side effects.

Nephrotoxicity

Lithium can cause nephrotoxicity after either short- or long-term treatment. Studies have found tubular atrophy, reduction in tubular function, and a decrease in the total number of sclerotic glomeruli in patients chronically treated with lithium. Studies have suggested that 15% to 20% of patients on long-term therapy develop a slow decline in glomerular filtration rate [43]. Progression to end-stage renal disease as a result of lithium is uncommon; however, in patients who progressed to end-stage renal disease there was an average of 20 years between the onset of therapy and end-stage

renal disease [44,45]. As the duration of therapy increases, so does the risk for renal impairment. Nephrogenic diabetes insipidus resulting in polyuria or polydipsia occurs in up to 20% of patients chronically taking lithium [43]. Lithium has also been associated with nephrotic syndrome (infrequently); more frequently it results in minimal change disease, whereas occasionally it is caused by focal-segmental glomerulosclerosis. Finally, the course of renal recovery following discontinuation of lithium is variable; some patients recover some renal function.

Drug-drug interactions are important to consider when examining renal complications of lithium therapy. Many drugs affect the serum levels of lithium. Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, thiazide diuretics, tetracycline, spectinomycin, metronidazole, and the cyclooxygenase-2 inhibitors all increase serum lithium levels. Aminophylline, theophylline, acetazolaminde, mannitol, and sodium bicarbonate can all decrease lithium levels. Given the many potential drug-drug interactions with lithium, it is essential to review concomitant medications, and to adjust lithium dosages accordingly as new interacting medications are added.

Hyponatremia

Hyponatremia is another side effect of psychotropics. Carbamazepine and oxcarbazepine are two of the agents frequently associated with hyponatremia. One study found prevalence rates of 29.9% and 13.5% for oxcarbazepine and carbamazepine, respectively [46]. Unfortunately, a clear mechanism has yet to be identified as a cause of drug-induced hyponatremia. Carbamazepine has also been reported in several cases as a cause of renal failure; no clear mechanism for this complication has been identified.

SSRIs are also frequently associated with hyponatremia, a finding that is often attributed to the syndrome of inappropriate anti–diuretic hormone secretion. Several risk factors have been associated with hyponatremia and SSRI use; these include older age, female gender, concomitant use of a diuretic, lower body weight, and low baseline sodium level. Prevalence rates for hyponatremia have varied widely (from 0.5%–32%) and most cases have occurred in patients over the age of 60 years [47]. In patients who have developed SSRI-associated hyponatremia, discontinuation of the drug has been a major part of treatment. Patients have been rechallenged after resolution of their symptoms, and some have had symptoms recur, whereas others have tolerated the medication without subsequent hyponatremia. There is no reliable way to predict what happens when medication is reintroduced.

Urinary dysfunction

Many psychiatric medications (including clozapine, mirtazapine, benztropine, SSRIs, and TCAs) have been associated with urinary retention,

urinary incontinence, or urinary frequency. This is generally thought to be mediated by anticholinergic effects. None of these medications, however, have been reported to cause these effects at rates above 1%.

Endocrinologic and metabolic

Weight gain

Weight gain with psychotropics is common and had generally been considered more of a nuisance until recent findings that link many of the atypical antipsychotics to significant weight gains, dyslipidemia, and diabetes [48–50]. Although the association between atypical antipsychotics and the so-called "metabolic syndrome" is not completely understood, studies have linked significant weight gain [48–50], dyslipidemia [50], and new-onset diabetes mellitus [51,52] to the use of clozapine and olanzapine and to quetiapine and risperidone (to a lesser extent). Several reports note diabetic ketoacidosis in patients who are taking clozapine or olanzapine but are without a history of diabetes [52]. The side effects of weight gain, hyperlipidemia, and diabetes are especially important in the critical care setting because they put patients at increased risk of cardiac, respiratory, and infectious comorbidities.

Thyroid dysfunction

Thyroid dysfunction (eg, hypothyroidism) is most commonly linked with the use of lithium. Lithium is thought to interfere with the production of thyroid hormones through a variety of mechanisms that are beyond the scope of this article. Women over the age of 50 years seem to be at increased risk of developing this side effect [53], although it may develop in either gender and in patients of any age. Treatment consists of either stopping lithium or administering thyroid hormone. Hyperthyroidism has also been associated with lithium use, although this side effect is far less common.

Hematologic

Blood dyscrasias

Many psychotropics have been associated with hematologic adverse events (including agranulocytosis, aplastic anemia, neutropenia, eosinophilia, and thrombocytopenia) [54]. The most important ones are highlighted in the following section.

Agranulocytosis is a rare (except with clozapine), but potentially quite serious, side effect of antipsychotics. The low-potency agents confer a higher risk than do the higher-potency agents [54]. Clozapine causes agranulocytosis most often; approximately 0.8% [55] of patients who take this medication are affected. It is most often seen in the first 6 months after starting the

medication. For this reason, use of clozapine in the United States requires registration in a national registry and weekly blood determinations. TCAs, MAOIs, and certain mood stabilizers (ie, carbamazepine and lamotrigine) have also been associated with agranulocytosis.

Carbamazepine is associated with potentially deadly agranulocytosis and aplastic anemia that is thought to be caused by direct bone marrow toxicity [56]. Valproic acid, however, can cause neutropenia, thrombocytopenia, and macrocytic anemia. Although there is no consensus on its frequency, a complete blood count should be checked periodically when these medications are used. Finally, lithium induces leukocyte proliferation and demargination and may be used to treat leukopenia from other causes.

Increased bleeding risk

SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) (like venlafaxine and duloxetine) are associated with bruising and with bleeding caused by inhibition of platelet function [57]. These effects have been associated with an increased risk of gastrointestinal bleeding, especially when taken in conjunction with aspirin or nonsteroidal anti-inflammatory drugs [58,59]. Reports of increased bleeding when SSRIs are taken in conjunction with warfarin [60] exist, although this link has not been firmly established.

Respiratory

Respiratory depression

Respiratory depression is the most common side effect of psychotropics on the respiratory system. This is seen primarily with benzodiazepines, because they alter the central nervous system's response to hypoxia. Longer-acting benzodiazepines are potentially more dangerous in this regard. Clinicians should also watch for the additive effects of other central nervous system depressants, including antipsychotics, sedating TCAs, and alcohol, among other agents. Those at particular risk include patients with an underlying obstructive sleep apnea; respiratory dysfunction; or acute illnesses (eg, pneumonia). In the medically ill, use of shorter-acting agents (eg, lorazepam) is advised.

Pulmonary embolism

Pulmonary embolism is a rare but serious complication linked with use of clozapine, olanzapine, risperidone, and quetiapine [61–66]. Deep venous thrombosis has also been associated with clozapine use, and the ziprasidone package insert lists pulmonary embolism as a possible side effect. A causal relationship, however, between these drugs and this complication has not been firmly established.

Dermatologic

Dermatologic side effects of psychotropics range from more common and relatively benign events (eg, sweating [from SSRIs and SNRIs]; acne [from lithium]; and alopecia [from lithium]) to serious adverse reactions (eg, drug-induced cutaneous reactions). This section focuses on the latter.

Rash and Stevens-Johnson syndrome

Toxic epidermal necrolysis and Stevens-Johnson syndrome are rare, potentially fatal, drug-induced cutaneous reactions that may be caused by mood-stabilizing medications (including carbamazepine and lamotrigine) [67,68]. The clinical manifestations include erosions of the mucous membranes, detachment of the epidermis, and severe constitutional symptoms [67] that may lead to death. Although benign rashes are seen in 5% to 20% of patients taking carbamazepine, lamotrigine, and valproate [5], the more serious syndromes are less common. The risk of developing Stevens-Johnson syndrome is highest during the first 2 months of treatment and at times of dose escalation. Patients who develop a rash on of these medications should stop their medication until a physician sees them.

Reproductive

A complete review of the effects of psychotropics used during pregnancy and the postpartum period is beyond the scope of this article; however, a brief review of the potential teratogenic risks for agents used in the critical care setting is warranted. Priapism, another potentially dangerous side effect of psychiatric medications, is then discussed.

Teratogenesis

Medications used to treat bipolar disorder, including anticonvulsants and lithium, have the greatest potential for teratogenic effects. The risk of fetal malformations depends on the time of fetal exposure and on the particular properties of the drug used. For example, exposure in the first 32 days of pregnancy may have an impact on neural tube development, whereas heart formation is affected during days 21 to 56, and development of the lip and palate is influenced by exposure during days 42 to 63 [69]. Lithium use during the first-trimester of pregnancy is most associated with Ebstein's anomaly (downward displacement of the tricuspid valve into the right ventricle with associated right ventricle hypoplasia) [69]. During later pregnancy, the concern with regard to maternal (and possibly fetal) toxicity is raised at the time of delivery because of a rapid decline in vascular volume. This can be avoided by decreasing (or stopping) lithium in the last several weeks of pregnancy [70]. Fetal

exposure to the anticonvulsants valproate and carbamazepine is associated with a twofold risk of neural tube defects (eg, spina bifida and anencephaly); craniofacial anomalies; microcephaly; growth retardation; and heart defects [69,71]. Lamotrigine, however, is generally preferred for treatment of bipolar disorder during pregnancy because of its lower association with fetal malformations [69,72].

Haloperidol is the preferred antipsychotic for use during pregnancy because it has been used for approximately 40 years and has a fairly extensive safety database for use in pregnancy [73]. As far as the use of newer atypical antipsychotics in pregnancy, there are little data available. One study, however, showed a higher proportion of low birth weight babies [74] when mothers were taking these medications during pregnancy. When contemplating use of antipsychotics, anticonvulsants, or lithium for women of child-bearing age in the critical care setting, it is essential to test for pregnancy and then make an informed decision while weighing the risks versus the benefits of treatment and choosing medications with lower risk profiles.

Priapism

Priapism (a sustained painful erection) is another serious side effect of psychotropics. Although trazodone is perhaps the best-known psychiatric medication associated with priapism, most of the antipsychotic medications can also be a cause [75]. Because priapism is underreported, rates of occurrence are not well understood. The major complication of priapism is fibrosis of the corpora cavernosa, which may result in impotence or abnormal erectile function if untreated within 4 hours of its onset [76]. Patients with sickle cell anemia, leukemia, hypercoaguable states, and autonomic dysfunction and cocaine-users, are at higher risk of developing priapism (because of low-flow states). Particular care should be taken when prescribing trazodone or antipsychotics in these populations. Priapism should be treated as a urologic emergency because of the potential morbidity, and patients taking these medications should be reminded to watch for development of this condition.

Summary

The use of psychiatric medications in hospitalized patients is an important component of comprehensive care. It is important, however, to be on the lookout for medical complications of psychiatric treatment that may result from direct medication toxicity, drug-drug interactions, or intoxication-withdrawal states. In this regard, it is essential to consider the potential complications of psychotropics while balancing the important role they serve in treatment of the medically ill.

References

[1] Nisijima K, Shioda K, Iwamura T. Neuroleptic malignant syndrome and serotonin syndrome. Prog Brain Res 2007;162:81–104.

[2] Ananth J, Parameswaran S, Gunatilake S. Side effects of atypical antipsychotic drugs. Curr Pharm Des 2004;10(18):2219–29.

[3] Caroff SN, Mann SC. Neuroleptic malignant syndrome and malignant hyperthermia. Anaesth Intensive Care 1993;21(4):477–8.

[4] Fricchione GL, Huffman JC, Stern TA, et al. Catatonia, neuroleptic malignant syndrome, and serotonin syndrome. In: Stern TA, Fricchione GL, Cassem NH, editors. Massachusetts General Hospital handbook of general hospital psychiatry. 5th edition. Philadelphia: Mosby; 2004. p. 513–30.

[5] Robinson MJ, Owen JA. Psychopharmacology. In: Levenson JL, editor. The American Psychiatric Publishing textbook of psychosomatic medicine. Arlington (VA): American Psychiatric Publishing; 2005. p. 871–922.

[6] Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352(11):1112–20.

[7] Gillman PK. The serotonin syndrome and its treatment. J Psychopharmacol 1999;13(1): 100–9.

[8] American Psychiatric Association. Diagnostic and statistical manual of mental disorders text revision (DSM-IV-TR). . 4th edition. Washington, DC: American Psychiatric Association; 2000.

[9] Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168(5):508–13.

[10] Marcangelo MJ, Ovsiew F. Psychiatric aspects of epilepsy. Psychiatr Clin North Am 2007; 30(4):781–802.

[11] Johnston JA, Lineberry CG, Ascher JA, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry 1991;52(11):450–6.

[12] Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007;62(4):345–54.

[13] Pisani F, Oteri G, Costa C, et al. Effects of psychotropic drugs on seizure threshold. Drug Saf 2002;25(2):91–110.

[14] Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006;14(3):191–210.

[15] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294(15):1934–43.

[16] Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 2005;330(7489):445.

[17] Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 2004;161(6):1113–5.

[18] Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353(22):2335–41.

[19] Haddad PM, Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. Hum Psychopharmacol 2008;23(Suppl 1):15–26.

[20] Noskin O, Jafarimojarrad E, Libman RB, et al. Diffuse cerebral vasoconstriction (Call-Fleming syndrome) and stroke associated with antidepressants. Neurology 2006; 67(1):159–60.

[21] Singhal AB, Caviness VS, Begleiter AF, et al. Cerebral vasoconstriction and stroke after use of serotonergic drugs. Neurology 2002;58(1):130–3.

[22] Singh H, Levinson DF, Simpson GM, et al. Acute dystonia during fixed-dose neuroleptic treatment. J Clin Psychopharmacol 1990;10(6):389–96.

[23] Tandon R. Safety and tolerability: how do newer generation atypical antipsychotics compare? Psychiatr Q 2002;73(4):297–311.
[24] Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991;158:503–10.
[25] Martin-Latry K, Goumy M, Latry P, et al. Psychotropic drugs use and risk of heat-related hospitalisation. Eur Psychiatry 2007;22(6):335–8.
[26] Alpert JE, Fava M, Rosenbaum JF. Psychopharmacologic issues in the medical setting. In: Stern TA, Fricchione GL, Cassem NH, editors. Massachusetts General Hospital handbook of general hospital psychiatry. 5th edition. Philadelphia: Mosby; 2004. p. 513–30.
[27] Mackin P. Cardiac side effects of psychiatric drugs. Hum Psychopharmacol 2008; 23(Suppl 1):3–14.
[28] Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993–2003. Drug Saf 2007;30(1):47–57.
[29] Killian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354(9193):1841–5.
[30] Prod Info Fazaclo orally disintegrating tablets, 2007.
[31] Prod Info Risperidal oral solution, 2007; Prod Info Risperidal Consta long-acting IM injection, 2007.
[32] Davydov L, Botts SR. Clozapine-induced hypersalivation. Ann Pharmacother 2000;34(5): 662–5.
[33] Koller EA, Cross JT, Doraiswamy PM, et al. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy 2003;23(9):1123–30.
[34] Bryant AE III, Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. Neurology 1996;46(2):465–9.
[35] Wadzinski J, Franks R, Roane D, et al. Valproate-associated hyperammonemic encephalopathy. J Am Board Fam Med 2007;20(5):499–502.
[36] Prod Info Serzone, 2001.
[37] Derby LE, Gutthann SP, Jick H, et al. Liver disorders in patients receiving chlorpromazine or isoniazid. Pharmacotherapy 1993;13(4):353–8.
[38] Schmidt S, Welcker M, Greil W, et al. Carbamazepine-induced systemic lupus erythematosus. Br J Psychiatry 1992;161:560–1.
[39] Zucker S, Zarrabi HM, Schubach WH, et al. Chlorpromazine-induced immunopathy: progressive increase in serum IgM. Medicine (Baltimore) 1990;69(2):92–100.
[40] Quismorio FP, Bjarnason DF, Kiely WF, et al. Antinuclear antibodies in chronic psychotic patients treated with chlorpromazine. Am J Psychiatry 1975;132(11):1204–6.
[41] Marraffa JM, Guharoy R. Lymphadenopathy secondary to lamotrigine (Lamictal). Vet Hum Toxicol 2002;44(5):276–7.
[42] Prod Info Cymbalta delayed-release oral capsules, 2007.
[43] Boton R, Gaviria M, Batlle DC. Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis 1987;10(5):329–45.
[44] Chugh S, Yager H. End-stage renal disease after treatment with lithium. J Clin Psychopharmacol 1997;17(6):495–7.
[45] Presne C, Fakhouri F, Noel LH, et al. Lithium-induced nephropathy: rate of progression and prognostic factors. Kidney Int 2003;64(2):585–92.
[46] Dong X, Leppik IE, White J, et al. Hyponatremia from oxcarbazepine and carbamazepine. Neurology 2005;65(12):1976–8.
[47] Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother 2006;40(9):1618–22.
[48] Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005; 80(1):45–53.

[49] Henderson DC. Diabetes mellitus and other metabolic disturbances induced by atypical antipsychotic agents. Curr Diab Rep 2002;2(2):135–40.
[50] Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157(6):975–81.
[51] Henderson DC. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence? CNS Drugs 2002;16(2):77–89.
[52] Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. J Clin Psychiatry 2007;68(4):533–41.
[53] Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. Clin Pract Epidemiol Ment Health 2006;2:23.
[54] Becker M, Axelrod DJ, Oyesanmi O, et al. Hematologic problems in psychosomatic medicine. Psychiatr Clin North Am 2007;30(4):739–59.
[55] Guzelcan Y, Scholte WF. [Clozapine-induced agranulocytosis: genetic risk factors and an immunologic explanatory model]. Tijdschr Psychiatr 2006;48(4):295–302 [in Dutch].
[56] Sedky K, Shaughnessy R, Hughes T, et al. Clozapine-induced agranulocytosis after 11 years of treatment. Am J Psychiatry 2005;162(4):814.
[57] Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med 2006;119(2):113–6.
[58] de Abajo FJ, Montero D, Rodriguez LA, et al. Antidepressants and risk of upper gastrointestinal bleeding. Basic Clin Pharmacol Toxicol 2006;98(3):304–10.
[59] Meijer WE, Heerdink ER, Nolen WA, et al. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med 2004;164(21): 2367–70.
[60] Skop BP, Brown TM. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. Psychosomatics 1996;37(1):12–6.
[61] Borras L, Eytan A, de Timary P, et al. Pulmonary thromboembolism associated with olanzapine and risperidone. J Emerg Med 2008;35(2):159–61.
[62] Lacut K, Le Gal G, Couturaud F, et al. Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism: results from the EDITH case-control study. Fundam Clin Pharmacol 2007;21(6):643–50.
[63] del Conde I, Goldhaber SZ. Pulmonary embolism associated with olanzapine. Thromb Haemost 2006;96(5):690–1.
[64] Yang TY, Chung KJ, Huang TL, et al. Massive pulmonary embolism in a young patient on clozapine therapy. J Emerg Med 2004;27(1):27–9.
[65] Parkin L, Skegg DC, Herbison GP, et al. Psychotropic drugs and fatal pulmonary embolism. Pharmacoepidemiol Drug Saf 2003;12(8):647–52.
[66] Pan R, John V, Hagg S. Clozapine and pulmonary embolism. Acta Psychiatr Scand 2003; 108(1):76–7 [discussion: 77].
[67] Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333(24):1600–7.
[68] Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007;68(20):1701–9.
[69] Yonkers KA, Wisner KL, Stowe Z, et al. Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 2004;161(4):608–20.
[70] Newport DJ, Viguera AC, Beach AJ, et al. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. Am J Psychiatry 2005;162(11):2162–70.
[71] Jones KL, Lacro RV, Johnson KA, et al. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med 1989;320(25): 1661–6.
[72] Morrell MJ. Pregnancy and antiepileptic drugs. Curr Neurol Neurosci Rep 2001;1(4): 359–60.

[73] Newport DJ, Calamaras MR, DeVane CL, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry 2007; 164(8):1214–20.
[74] McKenna K, Koren G, Tetelbaum M, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry 2005;66(4):444–9, quiz 546.
[75] Sood S, James W, Bailon MJ. Priapism associated with atypical antipsychotic medications: a review. Int Clin Psychopharmacol 2008;23(1):9–17.
[76] Jayaram G, Rao P. Safety of trazodone as a sleep agent for inpatients. Psychosomatics 2005; 46(4):367–9.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 657–722

CRITICAL
CARE
CLINICS

Delirium in the Acute Care Setting: Characteristics, Diagnosis and Treatment

José R. Maldonado, MD, FAPM, FACFE

Departments of Psychiatry and Medicine, Stanford University School of Medicine, 401 Quarry Road, Suite 2317, Stanford, CA 94305, USA

Delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, global cognitive impairment, disorientation, the development of perceptual disturbance, attention deficits, decreased or increased psychomotor activity (depending on the type of delirium), disordered sleep-wake cycle, and fluctuation in presentation (eg, waxing and waning). The term ''delirium,'' from the Latin roots *de* (meaning ''away from'') and *lira* (meaning ''furrow in a field'') and *ium* (Latin for singular), literally means ''a going off the ploughed track, a madness.'' The term ''delirium'' is reported to have been coined by the lay Roman writer Celsus (1AD) and described in his compendium *De Medicina* [1,2]. Clear descriptions of the syndrome are contained in Hippocrates's writings, who called the syndrome by the term *phrenitis* [3]. In 1813, the British physician Thomas Sutton introduced the term *delirium tremens* to designate delirium caused by the withdrawal from central nervous system (CNS) depressant agents, but which is almost exclusively applied in modern times to delirium resulting from alcohol withdrawal [4].

In the acute care setting, many names are used to describe the acute mental status changes associated with delirium. Commonly used terms include ''intensive care unit (ICU) psychosis'' or ''sundowning.'' The first describes the fact that mental status changes are often seen in the ICU, the second is a descriptor of a pattern by which subjects tend to experience confusion more frequently during periods of decreased or inappropriate stimulation, such as at night or ''sun down.'' The psychiatric literature uses other terms that usually describe common characteristics or features of the syndrome, such as ''acute confusional state'' (ie, acute, confusion) and ''acute brain failure'' to describe the gravity of the situation. Yet, neurologists and internists prefer the term ''encephalopathy,'' which literally means ''disease of

E-mail address: jrm@stanford.edu

doi:10.1016/j.ccc.2008.05.008 *criticalcare.theclinics.com*

the brain.'' The term encephalopathy is meant to convey a brain malfunction in the face of systemic metabolic derangements (eg, metabolic encephalopathy), cardiopulmonary or vascular problems (eg, hypoxic or hypertensive encephalopathy), renal disease (eg, uremic encephalopathy), liver disease (eg, hepatic encephalopathy), or endocrine disease (eg, Hashimoto's encephalopathy); or to be a consequence of toxic factors (eg, toxic encephalopathy or Wernicke's encephalopathy) or problems with oxygenation (eg, hypoxic encephalopathy). Unfortunately, the use of these various terms, even if accurate, may add to the confusion and difficulties of identifying and treating the syndrome of delirium.

Epidemiology of delirium

Delirium is the most common psychiatric syndrome found in the general hospital setting. Its prevalence surpasses most commonly known and identified psychiatric syndromes and varies depending on the medical setting. Table 1 compares the incidence of delirium in different medical settings and various psychiatric disorders [5]. The incidence of delirium among medically ill patients ranges from 10% in the general medicine ward to 85% in advanced cancer [6–11]. This wide range is associated with the organ system and disease process under consideration. For example, in the adult general medicine population the incidence of delirium ranges from 10% to 24%: as reported by Speed and colleagues 10.9% [12], Maldonado and colleagues 14% [13], Ritchie and colleagues 14.6% [14], and Gonzalez and colleagues 24% [15]. As expected, the incidence goes up with increased severity of illness, rising to 13% to 48% in after-stroke victims [16], 20% to 40% among HIV/AIDS patients [17,18], 60% in frail-elderly patients [19], 60% to 80% among patients in the medical ICU [20], and as high as 80% to 90% in terminally ill cancer patients [21]. One study found that 89% of survivors of stupor or coma progressed to delirium [22].

A European multinational study ($n = 3{,}608$) by Valdés and colleagues [23] found a delirium prevalence rate of 9.1% in the general hospital population. A Spanish study by Gonzalez and colleagues [15] confirmed findings in the United States and similarly suggested that the average hospital stay is prolonged from 12 days to 17.5 days when delirium is present. Similarly, a study conducted in Western Australia found a 10.9% prevalence rate of delirium among patients admitted to two general medicine wards ($n = 1{,}209$) [12].

Similarly, in the general surgical population the incidence of delirium is about 37% to 46% [24], and postoperative delirium has been described to occur in 10% to 60% of patients [25]. Again, the range in incidence of postoperative delirium depends on the type of surgery and the population studied: 25% to 32% among patients undergoing coronary artery bypass grafting (CABG); 50% to 67% among patients undergoing cardiotomy (eg, cardiac valve replacement) [26–29]; about 20% of elderly patients after

Table 1
A comparison of the incidence of psychiatric disorder in the general population and delirium among medically ill patients

Incidence of psychiatric disorders	% of general adult us population [5]	Incidence of delirium in selected medical populations	%
Major depression	6.7	General medicine wards	10–18
Dysthymic disorder	1.5	HIV/AIDS	30–40
Bipolar disorder	2.6	Medical-ICU	60–80
All mood disorders	9.5	General surgical wards (range)	37–46 (10–60)
		After stroke	13–48
Panic disorder	2.7	After CABG	25–32
OCD	1	After cardiotomy	50–67
PTSD	3.5	**Elderly**	
GAD	3.1	Out-patient minor (cataract) surgery	4.4
Social phobia	6.8	At time of hospitalization	10–15
Agoraphobia	8.7	In nursing homes	15–60
All anxiety disorders	18.1	After hip replacement	21–63
		In cancer patients	
Schizophrenia	1.1	General prevalence	25–40
Anorexia nervosa	0.5–3.7	Hospitalized cancer patients	25–50
Bulimia	2–5	Bone marrow transplant	73
Alzheimer's Disease	65–80 years old = 10% >80 years old = 50%	Advanced cancer	Up to 85

Abbreviations: CABG, coronary artery bypass graft surgery; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

Data from National Institute of Mental Health: Statistics on Mental Disorders in America. http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america.shtml. Accessed March 21 2008.

surgery for gynecologic malignancies [30]; 33% of patients undergoing abdominal aneurysm repair [31]; 12.5% in patients undergoing spine surgery [32]; 41% after bilateral knee replacement [33]; and 25% of elderly patients undergoing elective hip or knee replacement, compared with 65% after femoral neck fracture repair [34–36]. Acute mental status changes, neuropsychiatric dysfunction, and neurocognitive deficits are common after cardiac surgery [37]. Delirium and other forms of acute organic mental syndrome occurred in 32% to 80% of patients undergoing cardiac surgery [29,38,39].

The incidence of delirium is well documented in the acutely medically ill patient. A study by Ely and colleagues [20] involving patients admitted to the medical intensive care unit (MICU), 50% of which were receiving mechanical ventilation, found that 81.3% of MICU patients developed delirium during the course of their ICU stay. The mean onset of delirium was 2.6 days (standard deviation or SD $\pm$ 1.7), and the mean duration was 3.4 days (SD $\pm$ 1.9). The duration of delirium was associated with length of stay in the ICU ($r = 0.65$, $P = .0001$) and total length of hospital

stay (LOS) ($r = 0.68$, $P = .0001$). Multivariate analysis demonstrated that delirium was the strongest predictor of LOS in the hospital ($P = .006$), even after adjusting for severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration.

Maldonado and colleagues [13] found an 18% incidence of delirium in an acute ICU (eg, combined medical and surgical patients) based on *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria. As in previous studies, the average delirious patient age was over 65 years old and mostly male (60%). The presence of delirium significantly extended the overall length of stay (ie, 15 days in delirious patients, compared with 11 days in nondelirious counterparts).

Finally, delirium has been found to be the most common clinical neuropsychiatric condition in specialized palliative care units. It has been reported to occur in 26% to 44% of cancer patients admitted to hospital or hospice. As the disease progresses, over 80% of all advanced cancer patients eventually experience delirium in their final days [21,40].

Etiology of delirium

The syndrome of delirium is better thought of as having a multifactorial etiology, as is often the case in most medically ill patients. Patients in the ICU are usually critically ill, which makes them more susceptible to developing delirium. There are many risk factors known to contribute to the development of delirium.

Delirium clinical risk factors

- Age (greater than 75 years old)
- Baseline cognitive functioning:
  - 25% delirious are demented
  - 40% demented in hospital develop delirium
- Male gender
- Sensory impairment
- Use of intravenous lines, bladder catheters, and physical restraints
- Severe illness
  - Infections (particularly urinary tract infections and pneumonias, in older persons)
  - Hip fracture
  - Hyperthermia
  - Hypothermia
  - Hypotension and hypoperfusion
  - Hypoxia or anoxia
  - Malnutrition and nutritional deficiencies (eg, thiamine deficiency leading to Wernicke's encephalopathy)

- Metabolic disorders
  - Acute metabolic encephalopathies (eg, cardiac, hepatic and renal failure)
  - Acute vascular problems (eg, myocardial infarction, pulmonary embolism)
  - Endocrinopathies (eg, hyper- and hypothyroidism)
  - Water and electrolyte abnormalities
    - Hypo- or hyperglycemia
    - Hypo- or hypernatremia
    - Hypo- or hyperkalemia
    - Dehydration
- Elevation in serum cortisol levels
- CNS pathology (ie, stroke, intracranial hemorrhages, normal pressure hydrocephalus)
- Trauma (eg, severe physical trauma or surgery)

Exogenous substances

- Medication side effects:
  - Polypharmacy (more than three medications)
  - Psychoactive medications
    - Serotonergic agents
    - Anticholinergic agents
    - Over-the-counter substances
- Substance abuse and withdrawal
  - Alcoholism
  - CNS-depressant substances (both prescribed and illegal)
  - CNS-depressant withdrawal (eg, delirium tremens)
  - CNS-stimulant substances (both prescribed and illegal)
  - Hallucinogens
  - Over-the-counter substances
- Heavy metal poisoning
- Toxins (ie, toxic psychosis)

Sleep deprivation

Over-sedation

Pain, poorly controlled

Two of the known risk factors for delirium include the patient's age and the presence of a baseline cognitive disorder (eg, dementia, stroke). Studies have suggested that increasing age was an independent predictor of transitioning to delirium. A study of mehanically ventilated adults ($n = 275$) suggests that there is an incremental risk for transitioning into delirium for patients older than 65 years (odds ratio or OR of transitioning to delirium for age was 1.02 [1.00–1.03; $P = .04$]). In fact, the results suggest that for each additional year after age 65, the probability of transitioning to delirium increased by 2% (multivariable P values < 0.05) (Fig. 1) [41]. Similarly, a study of elderly patients undergoing hip surgery, found that mini-mental

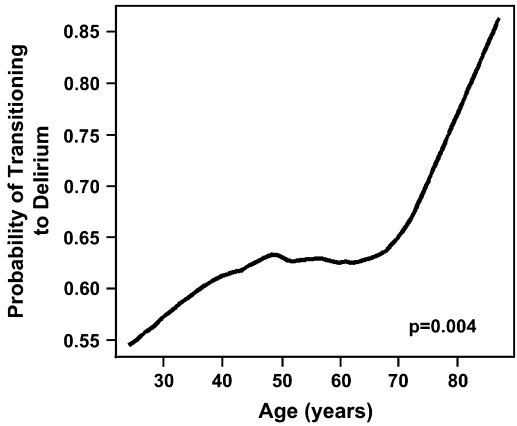

Fig. 1. Age and the probability of transitioning to delirium. The most notable finding related to age was that probability of transitioning to delirium increased dramatically for each year of life after 65 years. Adjusted OR 1.01 (1.00, 1.02) ($P = .03$). Y-axis = Probability; X-axis = Age in years. (*From* Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):23; with permission.)

state examination (MMSE) scores were identified as an independent predictor of postoperative delirium [42].

Milstein and colleagues [43] reported on the development of delirium among the elderly patient undergoing relatively simple outpatient surgery. They studied elderly patients ($n = 296$) undergoing cataract surgery and found a 4.4% incidence of postoperative delirium. As others have suggested, those developing delirium were older (82.1 versus 73.06 years; $P < .001$) and received higher benzodiazepine doses as pre-medication for surgery (69% versus 39.9%; $P < .002$).

In a prospective study evaluating neuropsychologic performance in older patients (ie, >70 years), subjects ($n = 100$) who were free of dementia and admitted for elective orthopedic surgery underwent a series of neuropsychiatric testing pre- and postoperatively [44]. Findings suggest that subtle preoperative attention deficits were closely associated with postoperative delirium. Patients who developed postsurgical delirium had significantly slower mean reaction times ($P \leq .011$) and greater variability of reaction time ($P = .017$) preoperatively. A four- to fivefold increased risk of delirium was observed for people one standard deviation above the sample means on these variables.

A study by Wahlund and Bjorlin [45] found that approximately 70% of elderly patients admitted to a specialized delirium ward had a pre-existing cognitive disorder, either dementia or mild cognitive impairment. Bergmann and Eastham [46] studied elderly patients ($n = 100$) admitted to an acute medical unit in a general hospital for the presence of psychiatric morbidity. They found that 7% suffer from dementia, while 16% suffered from acute

delirious states. Demented patients or patients suffering from other conditions associated with deficient brain function (ie, traumatic brain injury, drug and alcohol abuse and withdrawal) have a lower threshold for developing delirium and do so with greater frequency. Similarly, a study of elderly subjects undergoing hip or knee replacement ($n = 572$) demonstrated that the presence of dementia increased the occurrence of delirium [36]. Twenty four percent of subjects had preoperative dementia. Postoperatively, all (100%) of demented subjects developed delirium, compared with 31.8% in the nondemented population.

Poor oxygenation (ie, hypoperfusion and hypoxemia) has long been associated with the development of delirium, both because of medical problems as well as postoperatively. Severe illness processes, combined with both decreased oxygen supply and increased oxygen demand may lead to the same common end problem, namely decreased oxygen availability to brain tissue [47–50]. Inadequate oxidative metabolism may be one of the underlying causes of the basic metabolic problems initiating the cascade that leads to the development of delirium, namely: inability to maintain ionic gradients causing cortical spreading depression (ie, spreading of a self-propagating wave of cellular depolarization in the cerebral cortex) [51–56]; abnormal neurotransmitter synthesis, metabolism and release [57–65]; and a failure to effectively eliminate neurotoxic by-products [58,59,63].

A study of postthoracotomy patients demonstrated that 21% of the patients developed clinically significant postoperative delirium [66]. In this sample, delirium occurred in all patients who had inadequate oxygenation. The treatment of choice was supplementary oxygen, with a near perfect treatment success. Others have similarly linked delirium to the presence of poor oxygenation associated with untreated obstructive sleep apnea [67] and to the presence of occult hypoxia after total hip arthroplasty [68].

Of note, animal studies have suggested that subjects with baseline organic cerebral disorders, such as cerebrovascular disease, may be particularly sensitive to hypoxic injury. Miyamoto and colleagues [69] submitted laboratory animals to hypocapnia during surgical anesthesia, causing tissue damage in the caudoputamen. This model may suggest that a similar mechanism may be responsible for long-lasting postoperative delirium in patients with stroke or dementia.

Sleep is another factor that seems to play a significant role in developing delirium in the ICU. Sleep deprivation has long been linked to the development of delirium [70] and psychosis [71]. Studies have found that the average amount of sleep in ICU patients is limited to 1 hour and 51 minutes per 24-hour period [72]. Many factors may affect sleep in the ICU, including frequent therapeutic interventions, the nature of diagnostic procedures, pain, fear, and the noisy environment. Similarly, oversedation has been found to be an independent predictor of prolonged mechanical ventilation. In a prospective, controlled study ($n = 128$) of adults undergoing mechanical ventilation, subjects were randomized to either continuous sedation or daily

awakenings [73]. They found that the median duration of mechanical ventilation was 4.9 days in the intervention group (ie, daily awakening), as compared with 7.3 days in the control group ($P = .004$), and the median LOS in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P = .02$).

A great number of medications have been associated with an increased risk of delirium (Box 1). The highest incidence medication-induced delirium has been observed in patients taking more than three medications [74], medications with high psychoactive activity [75], and when drugs have high anticholinergic potential [76].

Medications with significant psychoactive effects have long been identified as a frequent cause of delirium. Several studies have linked the use of psychoactive agents to the etiology of 15% to 75% of delirium cases [19,21,77–81]. More specifically, opioids, corticosteroids, and benzodiazepines have been identified as major contributors to delirium in several studies (Fig. 2) [75]. Other medications, such as nonsteroidal anti-inflammatory agents, and chemotherapeutic agents, were also identified as causes of delirium.

There is significant evidence to suggest that there is a direct association between a medication's anticholinergic potential and their incidence of causing delirium [74,76,82–86]. Some drugs (eg, diphenhydramine, atropine) are easier to identify as having a high anticholinergic load. On the other hand, others are not so obvious. Several studies have demonstrated a direct relationship between a drug's anticholinergic potential (as measured by serum anticholinergic activity) and the development of delirium [76,85,87–90]. Tune has conducted several studies looking at the cumulative effect of drugs with subtle anticholinergic potential and their serum anticholinergic activity (Box 2, Table 2) [76,83,84,86,90,91].

Blazer and colleagues [92] conducted a study of the potential for anticholinergic toxicity among long-term care residents. Their study included residents aged 65 years and older ($n = 5{,}902$) who continuously resided in a nursing home for 1 year and determined drug administration and drug quantity. The survey revealed that 60% of residents received drugs with significant anticholinergic properties and nearly 10% of the residents received three or more medications with high anticholinergic load. Finally, Han and colleagues [93] followed medical inpatients ($n = 278$) and measured their exposure to anticholinergic medications. They found that exposure to anticholinergic agents was an independent risk factor for the development of delirium, and specifically associated with a subsequent increase in delirium symptom severity.

As suggested by many others, many gamma amino-butyric acid (GABA)-ergic medications have been implicated in the development of delirium [20,94–97]. It is now beginning to be understood that agents commonly used for achieving postoperative sedation may in fact contribute to delirium by (a) interfering with physiologic sleep patterns and (b) causing a centrally mediated acetylcholine deficient state (ie, interruption of central cholinergic

Box 1. Drugs believed to induce delirium

5-FU
Acetophenazine
Acyclovir
Aldesleukin
Alprazolam
Amandatine
Amidoarone
Amitriptyline
Amphetamine (in overdose)
Amphotericine B
Ampicillin
Anticonvulsants
Antihistamines
Antiparkinsonian Rx
Asparginase
Aspirin
Atropine
Azathioprine
Azithromycin
Barbiturates
Benzodiazepines (and ''paradoxical disinhibition'')
Benzquinamide
Beta-blockers
Betamethasone (and psychosis)
Bupropion
Cabergoline
Captopril
Cefalothin
Cefoxitin
Celecoxib
Cephalosporins
Chloramphenicol
Chlordiazepoxide
Chlorpromazine (and psychosis)
Chlorthalidone
Choline salicylate
Cimetidine
Ciprofloxacin
Clindamycin
Clioquinol
Clomipramine
Clozapine

(*continued on next page*)

Box 1 (*continued*)

Cocaine
Codeine
Corticosteroids
Cortisone (and psychosis)
Cotrimozazole
Cyclobenzaprine
Cycloserine
Cyclosporine
Desipramine
Dexamethasone (and psychosis)
Diazepam
Digoxin (and psychosis)
Diltoiazem
Dimenhydrinate
Diphenhydramine
Dipyridamole
Disulfiram (and mania and psychosis)
Dopamine
Doxepin
Droperidol
Ergotamine
Ethanol
Famotidine
Fentanyl
Fludarabine
Flurazepam
Furosemide
Gentamicin
Glutethimide
Halothane
Hydralazine
Hydrocortisone (and psychosis)
Hydrochlorothiazide
Hydroxyzine
Interleukin-2
Imipramine
Interferon
Isoflurane (and psychosis)
Isosorbide monotitrate
Itraconazole
Ketamine (and psychosis)
Ketoprofen

Levodopa/carbidopa (and psychosis)
Lidocaine
Lithium (and organic brain syndrome)
Lorazepam (and ''paradoxical disinhibition'')
Magnesium salicylate (and psychosis, headache, dizziness, drowsiness, confusion)
Monoamine oxidase inhibitors
Medazepam (and withdrawal syndromes)
Mefloquine
Memantine
Methohexital
Methyldopa
Methylprednisolone (and psychosis)
Methotrexate
Metrizamide
Midazolam
Mirtazapine
Nicotine (and withdrawal syndromes)
Nifedipine
Nitrazepam (and withdrawal syndromes)
Nitroprusside (and psychosis)
Nortriptyline
Opiates (and withdrawal syndromes)
Oxazepam
Oxycodone
Pancuronium
Paraldehyde
Paramethasone (and psychosis)
Paroxetine
Perazine
Perphenazine
Perphenazine/amitriptyline
Phenelzine
Phenobarbital (and withdrawal syndromes)
Phenytoin (and psychosis)
Piperacillin
Prednisolone (and psychosis)
Prednisone (and psychosis)
Promazine (and psychosis)
Propofol (and central a-chol synd)
Protriptyline (and central a-chol synd)
Quinidine
Rantidine

(*continued on next page*)

Box 1 (*continued*)

Rasagiline
Risperidone (and anxiety, depression, apathy)
Rofecoxib (and psychosis)
Scopolamine
Sodium salicylate
Sodium Thiosalicylate
Sympathomimetics
Tacrine
Tamoxifen
Tricylic antidepressants
Teceleukin (and psychosis, paranoia. fatigue, apathy, drowsiness, sleep disturbances)
Thophylline
Thiothixene
Tiaprofenic acid
Tobramycin
Trazodone
Triamcinolone (and psychosis)
Triamterene
Trimethobenzamide (central a-chol synd)
Triprolidine (and restlessness, insomnia, euphoria, nervousness, irritability, palpitations, nightmares, or seizures)
Vancomycin
Vincristine
Warfarin
Zolpidem
Zotepine (and anxiety, agitation)

Data from Electronic Physicians Desk Reference, 2007.

muscarinic transmission at the level of the basal forebrain and hippocampus) [95–97]. A study of blood and urine melatonin levels revealed an abolition of the circadian rhythm of melatonin release in deeply sedated ICU patients [98]. This suggests that sedative agents may contribute to the development of delirium by more than one mechanism (ie, disruption of sleep patterns; central acetylcholine inhibition; disruption of melatonin circadian rhythm). Therefore, it appears that commonly used sedative (eg, propofol, midazolam) may promote the development of delirium.

The irony is that these are the same medications physicians often use to manage agitated or delirious patients. This practice, even if immediately effective in tranquilizing a patient may, in the long run, aggravate and perpetuate the syndrome of delirium. One of the first studies to demonstrate the

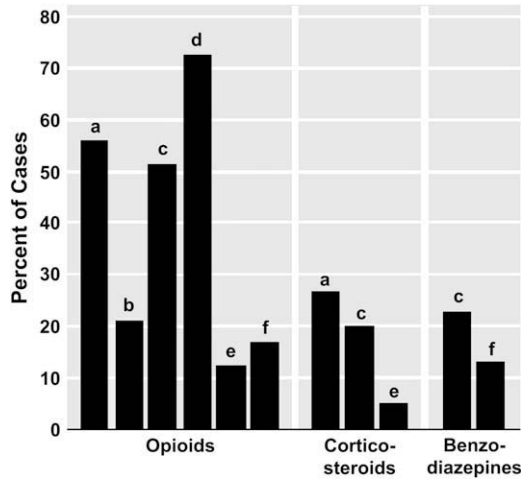

Fig. 2. Delirium cases potentially caused by opioids, corticosteroids and benzodiazepines in six case-series. [a]Breitbart and colleagues [78], [b]Morita and colleagues [80], [c]Tuma and DeAngelis [79], [d]Lawlor and colleagues [21], [e]Olofsson and colleagues [81], [f]Francis and colleagues [19]. (*From* Gaudreau JD, Gagnon P, Roy MA, et al. Association between psychotogenic medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005;46(4):304; with permission.)

relationship between benzodiazepine use and delirium was conducted by Marcantonio and colleagues [94]. They found that development of delirium was significantly associated with postoperative exposure to benzodiazepines (OR, 3.0; 95% confidence interval or CI, 1.3–6.8). These findings have been confirmed by Pandharipande and colleagues [41], who studied adult ventilated patients ($n = 275$) in the ICU for the development of delirium. They found that lorazepam was an independent risk factor for daily transition to delirium (OR, 1.2; 95% CI, 1.1–1.4; $P = .003$) (Fig. 3). These findings confirm many others who have previously suggested benzodiazepines to be culprits in the development of delirium and other cognitive impairment in medically ill patients [20,94,99,100]. Being aware of what types of medications a patient is taking and eliminating unnecessary medications can help reduce the potential for anticholinergic side effects.

As in the case with sleep, both pain and medications used for the treatment of pain have been associated with the development of delirium. Vaurio and colleagues [25] demonstrated that presence of postoperative pain is an independent predictor of delirium after surgery. Furthermore, they found a direct relationship between levels of preoperative pain and the risk for the development of postoperative delirium. On the other hand, the use of opioid agents has been implicated in the development of delirium [101–103]. Opioids are blamed for nearly 60% of the cases of delirium in patients with advanced cancer [40]. A study of cancer patients ($n = 114$) showed a significant associations between opioids and delirium, after controlling for other medications used [104]. Several studies have reported that patients

Box 2. Commonly used medicines that have anticholinergic effects

Antihistamines
Diphenhydramine
Hydroxyzine

Cardiovascular
Captopril
Chlorthalidone
Digoxin
Diltiazem
Dipyridamole
Furosemide
Hydrochlorothiazide
Hydralazine
Isosorbide mononitrate
Methyldopa
Nifedipine
Triamterene
Warfarin

Central nervous system
Alprazolam
Amitriptyline
Chlordiazepoxide
Codeine
Desipramine
Diazepam
Doxepin
Flurazepam
Imipramine
Oxazepam
Oxycodone
Phenelzine
Phenobarbital

Corticosteroids
Corticosterone
Dexamethasone
Hydrocortisone
Prednisolone

Gastroinitestinal
Atropine
Cimetidine
Ranitidine

Immunosuppression
Azathioprine
Cyclosporine

Infection
Ampicillin
Cefalothin
Cefamandole
Cefoxitin
Clindamycin
Cycloserine
Gentamicin
Piperacillin
Tobramycin
Vancomycin

Muscle relaxants
Pancuronium

Respiratory system
Theophylline

Data from Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62 Suppl 21:13.

who used oral opioid analgesics as their sole means of postoperative pain control were at decreased risk of developing delirium in comparison with those who used opioid analgesics via intravenous (IV) patient-controlled analgesia technique (OR, 0.4; 95% CI, 0.2–0.7) [25,103].

There is some data that suggests that some opioid agents may have greater deliriogenic potential than others. For example, several reports suggest that meperidine has a greater deliriogenic potential than other opioids [94,101,105]. Other studies have suggested that an opioid rotation from morphine to fentanyl has been associated with improved pain management and lower delirium rating scores [106]. Similarly, at least one case report suggests that the use of acetylcholinesterase inhibitors successfully reversed opioid-induced hypoactive delirium [107]. This may implicate an anticholinergic mechanism of opioid induced delirium.

Besides their potential anticholinergic effect or their disruption of sleep patterns, medications may cause delirium by disrupting thalamic gating

Table 2
Anticholinergic drug levels in 25 medications ranked by the frequency of their prescription for elderly patients

	Medication[a]	Anticholinergic drug level (ng/mL of atropine equivalents)[b]
1.	Furosemide	0.22
2.	Digoxin	0.25
3.	Dyazide	0.08
4.	Lanoxin	0.25
5.	Hydrochlorothiazide	0.00
6.	Propranolol	0.00
7.	Salicylic acid	0.00
8.	Dipyridamole	0.11
9.	Theophylline anhydrous	0.44
10.	Nitroglycerin	0.00
11.	Insulin	0.00
12.	Warfarin	0.12
13.	Prednisolone	0.55
14.	Alpha-methyldopa	0.00
15.	Nifedipine	0.22
16.	Isosorbide dinitrate	0.15
17.	Ibuprofen	0.00
18.	Codeine	0.11
19.	Cimetidine	0.86
20.	Diltiazem hydrochloride	0.00
21.	Captopril	0.02
22.	Atenolol	0.00
23.	Metoprolol	0.00
24.	Timolol	0.00
25.	Ranitidine	0.22

[a] At a 10–8 M concentration.
[b] = Threshold for delirium = 0.80ng/mL.
Data from Tune L, Carr S, Hoag E, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992;149(10):1393–4.

function (ie, the thalamus ability to act as a filter, allowing only relevant information to travel to the cortex). The cholinergic and the dopaminergic systems interact not only with each other but with glutamatergic and GABA pathways. Besides the cerebral cortex, critical anatomic substrates of psychotic pathophysiology would comprise the striatum, the substantia nigra/ventral tegmental area, and the thalamus. The thalamus can be understood as acting as a filter, usually allowing only relevant information to travel to the cortex. On the other hand, drugs of abuse (eg, phencyclidine, Ecstasy), as well as psychoactive medications frequently prescribed to hospitalized patients (eg, benzodiazepines, opioids, sympathomimetics, steroids) could compromise the thalamic gating function, leading to sensory overload and hyperarousal. Gaudreau and Gagnon [108] have propose that drug-induced delirium would result from such transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABAergic, dopaminergic, and cholinergic pathways at critical sites of action.

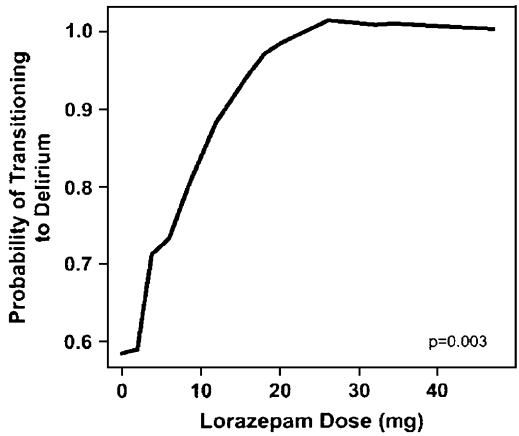

Fig. 3. Lorazepam and the probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 hours. This incremental risk was large at low doses and plateaued at around 20 mg per day. Y-axis = Delirium risk; X-axis = Lorazepam dose (in mg). (*From* Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):21–6; with permission.)

There are several surgical procedures known to increase the risk of developing delirium, presumably because of the complexity of the surgical procedure, the extensive use and type of intraoperative anesthetic agents, and potential postoperative complications [109]. For example, in cases of cardiac surgery the following factors have been associated with the increased risk for delirium: the use of cardio-pulmonary by-pass (CPB) (eg, hypoperfusion, embolic load), management strategies (eg, pH stat versus alpha stat, on-pump versus off-pump) or to the type of procedure (eg, intracardiac versus extracardiac) [39,110–112]. In the case of orthopedic procedures, fat embolism, blood loss, older age, and the type of anesthetic agent used have all been associated with a greater risk of delirium [105,113,114].

Certain psychiatric diagnoses, including a history of alcohol and other substance abuse (6.9%), as well as schizophrenia and bipolar disorder (up to 14.6%) have also been associated with a higher incidence of delirium [14,115].

Finally, the severity of the patient's underlying medical problems has a significant role in the development and progression of delirium. Pandharipande and colleagues [41] found that increased severity of illness, as measured by the modified Acute Physiology and Chronic Health Evaluation (APACHE) II (ie, removing the Glasgow Coma Scale) is associated with a greater probability of transitioning to delirium. Furthermore, it indicated that the incremental risk becomes larger until reaching a plateau APACHE score of 18 (Fig. 4). The adjusted odds ratio of transitioning to delirium for APACHE II score was 1.06 (1.02–1.11; $P = .004$). This odd ratio suggests that for each additional APACHE II score, the probability of transitioning to delirium increased by 6%. Similarly, in a study of elderly patients

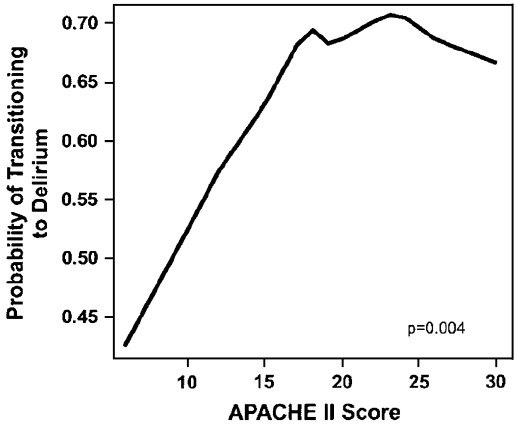

Fig. 4. Severity of illness and the probability of transitioning to delirium. The probability of transitioning to delirium increased dramatically for each additional point in APACHE II severity of illness score until reaching a plateau APACHE score of 18. (*From* Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):21–6; with permission.)

undergoing hip surgery, APACHE II scores were identified as an independent predictor of delirium [42].

Mortality and morbidity of delirium

According to the latest statistics (2006) from the Society of Critical Care Medicine, there are 5,980 ICUs in the United States, caring for approximately 55,000 patients per day [116]. The incidence of delirium in the ICU has been reported to be as high as 81.3% [20]. Several studies have found that patients who developed delirium fare much worse than their nondelirious counterparts when controlling for all other factors. One study [19] found that the mortality rate was higher among delirious patients, as high as 8% (compared with 1% in nondelirious patients). In another study, ICU-patients who developed delirium had higher 6-month mortality rates (34% versus 15%, $P = .03$) (Fig. 5) [117]. Similarly, another study found that the 90-day mortality was as high as 11% among delirious patients, compared with only 3% among nondelirious elderly patients [118].

Not only is delirium associated with an increased mortality, but the rate of morbidity is also increased. Multiple studies have demonstrated that delirious patients have prolonged hospital stays (ie, average 5–10 days longer), compared with patients suffering from the same medical problem who do not develop delirium as a complication [13,19,20,117]. Similarly, a study of psychiatric inpatients demonstrated that the hospital stays of patients with delirium were 62.1% longer than those of patients without delirium [14].

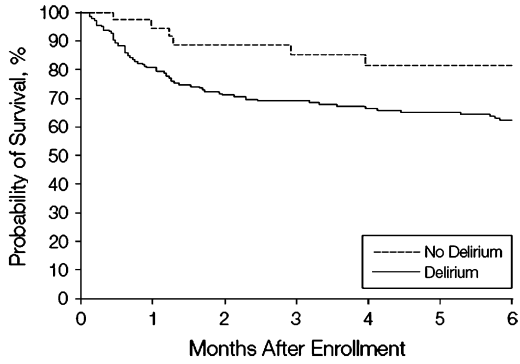

Fig. 5. Analysis of delirium in the ICU and 6-month survival. (*From* Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1758; with permission.)

There are concerns regarding the long-term effects of delirium. It has been estimated that about 40% of delirium cases develop some form of chronic brain syndrome [118]. Some have suggested that the functional decline observed during the acute delirious state may persist 6 months or longer after discharge from the hospital [119]. In fact, Maldonado and colleagues [13] found that only about 14% of those patients who developed delirium returned to their baseline level of cognitive functioning by the time of discharge from the hospital. Levkoff and colleagues [120] found an even lower rate of recovery. In their sample, only 4% of delirious patients experienced full resolution of all symptoms of delirium before discharge from the hospital. After following this sample longitudinally, they found that an additional 20.8% achieved resolution of symptoms by the third month after hospital discharge; and an additional 17.7% by the sixth month after discharge from the hospital. Furthermore, a study by Newman and colleagues [121] reported that cognitive deficits at discharge were significantly associated with poor long-term cognitive functioning for up to 5 years after cardiac surgery. This may explain why patients who develop delirium while in the hospital have a greater need for placement in nursing homes or rehabilitation facilities instead of returning home (16% versus 3%) [19,122]. Others have also suggested that elderly patients who develop delirium "are never the same" even after they recover from the acute event [118,120,123].

Fann and colleagues [124] looked at the impact of delirium on cognition in myeloablative hematopoietic stem-cell transplantation (HSCT) patients ($n = 90$). All patients completed a comprehensive battery of neuropsychiatric testing before receiving their HSCT and were subsequently followed for 30 and 80 days after transplantation. After adjusting for confounding factors, patients who experienced delirium after HSCT had significantly worse executive functioning (beta $= -1.1$; $P < .02$), and worse attention and

processing speed postoperatively (beta = −4.7 and −5.4, respectively) compared with those who did not experience delirium.

In addition to a patient's increased morbidity and mortality, increased risk of delivery of care to medical and nursing staff, and causing distress to the patient, the family, and medical caregivers, the development of postoperative delirium has been associated with greater care costs, poor functional and cognitive recovery, and prolonged hospital stays [117,125,126]. An increasingly recognized phenomena is the development of posttraumatic stress disorder (PTSD) secondary to the dramatic and bizarre delusional and hallucinatory experiences that occur during a delirious state. The theory behind this phenomenon is that the strong emotional tone of the frightening delusions may have contributed to the development of PTSD, particularly in individuals with no factual recall of their ICU stay [78,127–130].

The economic impact of delirium is substantial, rivaling the health care costs of falls and diabetes mellitus. Maldonado and colleagues [13] conducted a retrospective chart review of all patients who experienced delirium on a step-down critical care unit. The sample of medical and surgical patients ($n = 254$) included all subjects admitted to the unit over a predetermined, 60-day period. Delirious patients were initially identified from a nursing log of patients who manifested symptoms of delirium. Medical records were extensively reviewed to validate whether delirium occurred, and registered the duration of symptoms and the treatment regimen applied in each case. Supporting data included two or more of the following: administration of antipsychotic agents or a benzodiazepine for the management of agitation or psychosis, use of a sitter or physical restraints for the management of confusion or agitation, and results of cognitive function assessment methods (eg, MMSE, Delirium Rating Scale or DRS). Overall, 14% of patients developed delirium during their ICU stay. Collectively, all patients had a total of 1,471 inpatient days. Delirious patients were reported to be symptomatic for a total of 318 days. Thus, even though they were only 14% of the entire critical care unit population, they used 22% of the total inpatient days. Men were over-represented among all admissions to the unit (61%); however, the proportion of men manifesting delirium was statistically identical to that of the nondelirious patient group (chi square = 0.757, $P = .38$). The average number of days from symptomatic onset to resolution was 10.8 days for untreated patients and 6.3 days for treated patients. As a group, delirious patients were older (71.3 versus 63.6 years), remained hospitalized longer (16.4 versus 6.6 days), and represented greater total costs per case ($63,900 versus $30,800).

Similarly, Leslie and colleagues [131] studied hospitalized elderly patients and looked at the difference in health care costs for those developing delirium. Regression models were used to determine costs associated with delirium after adjusting for patient sociodemographic and clinical characteristics. In their sample ($n = 841$), 13% of patients developed delirium during the index hospitalization. Patients with delirium had significantly higher

unadjusted health care costs and survived fewer days. After adjusting for pertinent demographic and clinical characteristics, average costs per day survived among patients with delirium were more than 2.5 times the costs among patients without delirium. Total cost estimates attributable to delirium ranged from $16,303 to $64,421 per patient. Another study demonstrated that in patients who developed delirium in the ICU, the health care costs were 31% higher than for patients with similar medical problems but without delirium ($41,836 versus $27,106) [126]. The national burden of delirium on the health care system has been estimated to range from $38 billion to $152 billion each year [131].

Diagnosing delirium

Despite its high prevalence, delirium remains unrecognized by most ICU clinicians in as many as 66% to 84% of patients experiencing this complication [19,132]. Several studies have demonstrated that hospital staff in general and physicians in particular are not good at identifying delirium. Often, mental status changes associated with delirium are misattributed to dementia, depression, or just an expected occurrence in the critically ill patient. A study by Farrell and Ganzini [133] found that about 41.8% of subjects referred to the psychiatry consultation service for depression were in fact delirious, highlighting how easy it is to misdiagnose this condition. Similarly, Kishi and colleagues [134] looked at the rate of missed diagnosis of delirium by general medicine and surgical services. Again, they found these services missed the diagnosis of delirium in 46% of requested psychiatric consultations (ie, they called psychiatric consultations for reasons other than delirium, but delirium was the cause for the behavior for which the consult was requested). The factors associated with their failure to identify delirium accurately were first, the presence of a past psychiatric diagnosis, which the primary team used to explain delirium symptoms; and second, the presence of pain.

Eissa and colleagues [111] followed patients ($n = 48$) after cardiac surgery for signs of postoperative confusion. Subjects were assessed by a nonstructured physician interview, and by the short portable mental status questionnaire (SPMSQ). The ''ward interviews'' involved informal dialogue between the patients and medical staff during routine ward visits. There was no structured format to the questions asked by the physician, although standard clinical management includes assessment of the subject's orientation to time, place, person, and dialogue. Ultimately, the presence or absence of confusion was based solely on the medical staff's subjective decisions. The nonstructured physician interview detected confusion in only 2% of the subjects, whereas the SPMSQ diagnosed confusion in 31% of them. The nonstructured ward interviews failed to detect confusion in 14 of the 15 subjects (93%) detected by the SPMSQ and also provided no standardized means by which to classify the degree of confusion. This study highlights

the need to actively assess for the presence of delirium in medically ill patients. These findings are similar to those of Rolfson and colleagues [135], who followed 71 patients after cardiac surgery to detect the incidence of delirium using the Confusion Assessment Method (CAM) [136], the MMSE [137], the clock drawing technique [138,139], and DSM-III-R (revised) criteria [140]. They found that delirium was present in 32.4% of subjects.

The lack of recognition may be worsened by medical personnel's unawareness of the patient's pre-existing cognitive deficits. In a study of elderly patients (ie, older than 65) ($n = 165$) admitted to the ICU, researchers assessed patients and interviewed their families for evidence of pre-existing cognitive deficits. They found that the prevalence of pre-existing cognitive impairment was 38%. Yet ICU attending physicians were unaware of the existence of these in 53% of the cases. The number was similar (59%) for resident physicians [141]. As previously discussed, the presence of cognitive deficits predicts a greater occurrence of delirium; thus, it is important for physicians to know the substrate they are working with and institute techniques that would minimize delirium in populations at risk.

Overall, the most important aspects of accurate diagnosis are vigilance and a high level of suspicion, particularly in patients at higher risk. The diagnostic gold standard for delirium is the *Diagnostic and Statistical Manual for Mental Disorders*, Fourth edition, text revised (TR) (Box 3) [142].

There are a number of clinically available instruments (Box 4) developed to assist nonpsychiatric personnel in screening for the presence of delirium. These instruments were designed to help nonpsychiatrists (eg, nurses,

Box 3. DSM-IV-TR diagnostic criteria for delirium

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (eg, memory deficit, disorientation, language disturbance) or
C. Development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
D. Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

Data from APA, Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994. p. 129.

Box 4. Objectives measures for the diagnosis of delirium

DSM-IV-TR (Gold Standard; APA 1994) [142]
Cognitive Test for Delirium (CTD) (Hart, et al 1996) [271]
Confusion Assessment Method (CAM) (Inouye, et al) [136]
Confusion Assessment Method for the Intensive Care unit (CAM-ICU) (Ely, et al) [145]
Confusional State Evaluation (CSE) (Robertsson, et al 1997) [272]
Delirium Assessment Scale (DAS) (O'Keeffe 1994) [273]
Delirium Detection Score (DDS) (Otter, et al 2005) [274]
Delirium Index (DI) (McCusker, et al 1998) [275]
Delirium Rating Scale (DRS) (Trzepacz, et al 1988) [144]
Delirium Rating Scale-revised-98 (DRS) (Trzepacz, et al 2001) [146]
Delirium Severity Scale (DSS) (Bettin, et al 1997) [276]
Delirium Symptom Interview (DSI) (Albert, et al 1992) [277]
Memorial Delirium Assessment Scale (MDAS) (Breitbart, et al) [211]
Short portable mental status questionnaire (SPMSQ) (Pfeiffer 1975) [278]

Brief tests of cognitive functioning
Mini-Mental State Examination (MMSE) (Folstein, et al) [137]
Modified Mini-Mental State Examination (3MS) (Bland, et al 2001) [279]
Trail-Making, A and B (O'Donnell 1983) [280]

internists and research assistants) diagnose delirium [143,144]. All these scales (eg, CAM [136], CAM-ICU [145], DRS [144], and DRS-98 [146]) have been derived from, and validated against expert psychiatric opinions and the DSM diagnostic criteria. Unfortunately, these tools have a high false-positive rate (as high as 10%), thus the team that developed the instrument recommends that all patients identified as delirious by screening instruments "have a complete clinical evaluation to confirm the diagnosis" [136,147]. The most critical part of the assessment, given the characteristic waxing and waning of this syndrome, is to add the interview of the family members, nursing and medical staff, and a thorough review of the chart for behaviors exhibited during the preceding 24 hours to the clinical examination. The DRS was administered by the study's research assistant and used only as a confirmatory measure.

Another potential clue of the presence of delirium may come from a thorough neuropsychiatric examination. In the author's experience, patients with delirium tend to exhibit a re-emergence of primitive signs (Box 5). This appears to be more consistent in cases of hypoactive delirium. The

Box 5. Primitive reflexes

These are clinical features that indicate brain dysfunction but that cannot be precisely localized or lateralized. When present, these signs suggest cortical disease, especially frontal cortex, resulting in disinhibition of usually extinguished or suppressed primitive reflexes. Their clinical significance is uncertain and is difficult to correlate with psychiatric illnesses and other behavior disorders, including delirium.

Glabellar reflex: with the examiner's fingers outside of patient's visual field, tap the glabellar region at a rate of one tap per second. A pathologic response is either absence of blink, no habituation, or a shower of blinks. Normal response equals blinking to the first few taps with rapid habituation.

Rooting reflex: tested by stroking the corner of the patient's lips and drawing away. Pursing of the lips and movement of the lips or head toward the stroking is a positive response.

Snout reflex: elicited by tapping the patient's upper lip with finger or percussion hammer causing the lips to purse and the mouth to pout.

Suck reflex: tested by placing your knuckles between the patient's lips. A positive response would be puckering of the lips.

Grasp reflex: elicited by stroking the patient's palm toward fingers or crosswise while the patient is distracted, causing the patient's hand to grasps the examiner's fingers.

Palmomental reflex: test by scratching the base of the patient's thumb (noxious stimulus of thenar eminence). A positive response occurs when the ipsilateral lower lip and jaw move slightly downward, and does not extinguish with repeated stimulation.

Babinski sign: downward (flexor response) movement of the great toe in response to plantar stimulation.

Adventitious motor overflow: seen as the examiner tests one hand for sequential finger movements, and the fingers of the other hand wiggle or tap. Also, if there are choreiform movements.

Double simultaneous stimulation discrimination: tested with the patient's eyes closed. The examiner simultaneously brushes a finger against one of the patient's cheeks and another finger against one of the patient's hands, asking the patient where he has been touched.

relationship between poor cognitive status and primitive reflexes has been described in patients suffering from HIV-related cognitive disorders [148] and in cases of dementia [149]. There is at least one study describing the presence of primitive reflexes in postcardiotomy patients suffering from postoperative neuropsychiatric complications [150]. Further studies are needed to determine whether an assessment for the presence of primitive reflexes may add to the diagnostic accuracy for delirium, or at least assist in the characterization of delirium type, or whether it has any prognostic value.

Some have advocated the use of the electroencephalogram (EEG) as a way to identify and diagnose delirium. Engel and colleagues [151] were the first to describe the relationship between delirium and the diffuse slowing and progressive disorganization of rhythm seen in the EEG. The most common EEG findings in delirium include slowing of peak and average frequencies, and decreased alpha activity but increased theta and delta waves. Studies suggest that EEG changes correlate with the degree of cognitive deficit, but there does not appear to be a relationship between EEG patterns and delirium motoric type [152–160]. The clinical usefulness of EEG in the diagnosis of delirium may be limited by its limited specificity (given there are a number of conditions and medications that may affect the EEG) and the practicality of conducting the test (particularly in the case of agitated and combative patients). Still, the EEG may provide useful in differentiating delirium from other psychiatric and neurologic conditions, such as catatonic states, seizure activity, somatoform disorders, and malingering.

The most critical part of the assessment, given the characteristic waxing and waning of this syndrome, is to obtain as much information and from as many sources as possible (eg, interview of family members, nursing and other medical staff), coupled with a thorough review of the chart for behaviors exhibited during the preceding 24 hours to the clinical examination.

Delirium subtypes

Liptzin and Levkoff [147] were the first to characterize the different types of delirium based on behavioral characteristics (Table 3). Others have confirmed the presence of these motoric subtypes. According to these studies, there are at least three types of delirium based on their clinical manifestations: hyperactive, hypoactive, and mixed (Fig. 6) [161,162]. The most common type is the mixed form (46%), followed by the hyperactive (30%) and the hypoactive (24%). To most physicians, the most clear and recognizable form is the hyperactive type. Most clinicians agree that a confused, disoriented patient who does not have a pre-existing psychiatric diagnosis, who suddenly becomes agitated, combative, or assaultive, is probably suffering from the hyperactive or ''agitated type'' of delirium. The term ''mixed type'' is used to describe the classic ''waxing and waning'' pattern, commonly seen in medically ill patients who appear agitated and combative at times, with alternating episodes of somnolence and hypoactivity.

Table 3
Delirium subtypes

Hyperactive (three or more)	Hypoactive (four or more)
Hypervigilance	Unawareness
Restlessness	Lethargy
Fast/loud speech	Decreased alertness
Anger/irritability	Staring
Combativeness	Sparse/slow speech
Impatience	Apathy
Uncooperative	Decreased motor activity
Laughing	
Swearing/singing	
Euphoria	
Wandering	
Easy startling	
Distractibility	
Nightmares	
Persistent thoughts	

Data from Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161:843–5.

The most difficult type of delirium to identify is the hypoactive type. Classically, these patients present with symptoms that are commonly associated with depression [147]. These include unawareness of the environment, lethargy, apathy, decreased level of alertness, psychomotor retardation, decreased speech production, and episodes of unresponsiveness or staring. Patients with hypoactive delirium often endorse depressive symptoms, such as low mood (60%), worthlessness (68%), and frequent thoughts of death (52%) [133]. Studies have demonstrated that a large percentage of these patients are inappropriately diagnosed and treated as depressed [133]. The author's own experience at Stanford University Hospital parallels that of others [133,134]. Maldonado and colleagues [13] found that 42% of

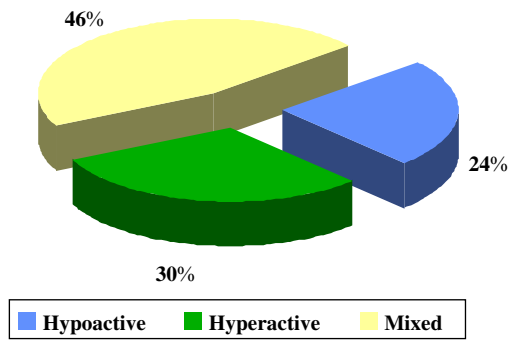

Fig. 6. Motoric subtype of delirium. (*Data from* Meagher DJ, O'Hanlon D, O'Mahony E, et al. Relationship between symptoms and motoric subtype of delirium. J Neuropsychiatry Clin Neurosci 2000;12(1):51–6.)

the time when the psychiatry consultation service was called to treat a patient for "depression," the patient's correct diagnosis was hypoactive delirium. The same study found that nearly 80% of these patients had been inappropriately prescribed antidepressant medications.

Management of delirium

Clinicians have three potential approaches when it comes to the management of delirium: (1) managing delirium (ie, symptomatically managing behavioral dyscontrol, such as agitation and psychosis); (2) treatment of delirium (ie, directly addressing either the underlying causes and the neurochemical cascade triggered by the underlying cause itself); or (3) prevention of delirium (ie, use of techniques or methods, either pharmacologic or behavioral, with the purpose of avoiding the development of delirium). This section covers the first; the following section addresses the third. The second section is covered in the article by Dr. Maldonado, elsewhere in this issue.

The adequate treatment of delirium includes the following steps: (1) accurate diagnosis of the condition (eg, hypoactive delirium versus depression), (2) management of the behavioral and psychiatric manifestations and symptoms to prevent the patient from self-harm or harming of others, (3) identification of the etiologic causes of delirium, and (4) treatment of underlying medical problems. Adequate medical management begins with timely diagnosis and early intervention, as shown in the following algorythm for the prevention and management of delirium.

Algorithm for the prevention and management of delirium

I. Be vigilant for the possibility of delirium.
   A. Obtain baseline level of cognitive functioning information from accessory sources.
   B. Screen for the development of delirium in high risk groups, either by the use of psychiatric consultants or objective scales (eg, DRS-98; CAM).
   C. Use psychiatric consultants to help with assessment and design of the treatment plan, if available.
II. Identify and treat underlying medical causes.
III. Non-Pharmacological Treatment Strategies:
   A. Correct malnutrition, dehydration and electrolyte abnormalities should be corrected as quickly and safely as possible.
   B. Remove immobilizing lines and devices (ie, IV lines, chest tubes, bladder catheters and physical restraints) as early as possible.
   C. Correct sensory deficits (ie, eyeglasses, hearing aids).
   D. Promote as normal a circadian light rhythm as possible. Better if this can be achieved by environmental manipulations, such as light

control (ie, lights on & curtains drawn during the day; off at night) and noise control (ie, provide ear plugs, turn off TVs, minimize night staff chatter), rather than by the use of medications.

E. Provide adequate intellectual and environmental stimulation as early as possible.

F. Minimize environmental isolation.

IV. Pharmacological Treatment Strategies:

A. Conduct an inventory of all pharmacological agents been administered to the patient. Any medication or agent known to cause delirium (see Table C) or to have high anticholinergic potential (see Table G) should be discontinued, if possible, or a suitable alternative instituted.

B. Avoid using GABAergic agents to control agitation, if possible. Exceptions: cases of CNS-depressant withdrawal (ie, alcohol, benzodiazepines, barbiturates) or when more appropriate agents have failed and sedations is needed to prevent patient's harm.

C. Adequately assess and treat pain.

D. Avoid the use of opioids for behavioral control of agitation.

E. For the pharmacological management of delirium (all types) consider using:

i. Acetylcholinesterase inhibitor (eg, rivastigmine, donepezil, physostigmine, rivastigmine) for correction of central anticholinergic syndrome.

ii. Serotonin antagonist (eg, ondansetron) to control toxic elevations of 5-HT usually associated with hypoactive delirium, although some studies have suggested its use may be indicated in all types of delirium.

iii. Rotate opioids from morphine and meperidine to fentanyl or hydromorphone.

iv. Melatonin or melatonin agonists (eg, ramelteon) to promote a more natural sleep.

v. Dopamine agonists to manage the theorized abnormally elevated levels of dopamine, and provide restoration of putative hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis, primitive reflexes), as well as to protect neurons against hypoxic stress and injury. The dose of dopamine antagonist use may depend on the type of delirium been treated.

vi. Alpha-2 agonists (eg, dexmedetomidine, clonidine), for protection against the acute NE released secondary to hypoxia or ischemia, leads to further neuronal injury and the development of worsening of delirium.

vii. NMDA-receptor blocking agents, to minimize glutamine induced neuronal injury (eg, amantadine, memantine).

F. In case of hyperactive delirium:
   i. Use low to moderate dose haloperidol (eg, < 20mg/24hr), if the patient's cardiac condition allows it and there are no significant electrolyte abnormalities.
      a. Before using haloperidol: obtain 12-lead ECG; measure QTc & electrolytes. Correct K+ & Mg+, if needed.
      b. If possible avoid other medications known to increase QTc and/or inhibitors of CPY3A4.
      c. Discontinue its use if QTc increases to >25% of baseline or >500msec.
   ii. When the use of haloperidol is contraindicated or not desirable, atypical antipsychotics should be considered:
      a. Better evidence for: risperidone, quetiapine.
      b. Limited data for: olanzepine, aripripazole, perospirone.
      c. Avoid: clozapine, ziprasidone.

G. In case of hypoactive delirium:
   i. Evidence suggests that DA antagonists may still have a place given the excess DA theory.
      a. If haloperidol is use, recommended doses are in the very low range (ie, 0.25 to 1mg / 24hr).
      b. If an atypical is preferred, consider an agent with low sedation (ie, risperidone); unless a sedative agent is needed to restore sleep-wake cycle not responding to E-iv (see above).
   ii. In cases of extreme psychomotor retardation or catatonic features, in the absence of agitation or psychosis, consider the use of psychostimulant agents (eg, methylphenidate, dextroamphetamine, modafinil) or conventional dopamine agonists (eg, bromocriptine, amantadine, memantine).

Nonpharmacologic treatment strategies

Given the findings reported by Inouye and colleagues [74,163], a multicomponent approach is recommended; targeting identified, treatable contributing factors must be undertaken early. As mentioned above, given the high rate of under and missed diagnosed cases, vigilance and a high level of suspicion is essential, particularly in high-risk patients. The routine use of assessment scales or diagnostic interviews by properly trained personnel is key both in prevention and timely treatment. Early involvement of the Psychosomatic Medicine team (Psychiatry) or a Geropsychiatric service has been shown to be extremely valuable, both in prevention and early intervention. An active search for possible etiologies of delirium must first attempt to rule out the common causes of the syndrome (see list titled ''Delirium clinical risk factors'' above). This must include a review of all medications and identification and possible discontinuation of agents with

high deliriogenic potential (see Box 1). Appropriate diagnostic tests and assays should be ordered and reviewed in a timely fashion, and all abnormal findings addressed accordingly.

Immobilizing lines and devices (eg, chest tubes, IV lines, bladder catethers) should be removed as early as possible. Similarly, physical restraints should be avoided and eliminated as soon as it is safe to do so. Early correction of sensory deficits should be undertaken. That is, eyeglasses and hearing aids should be replaced or fitted (if not using them before the hospitalization) as soon as possible. This will allow patients to familiarize themselves with the environment and reorient themselves early on. It will also minimize the occurrence of misperceptions or misinterpretation of environmental cues and stimuli. Environmental isolation should be minimized if possible. Family members and loved ones should be encouraged to visit and provide a familiar and friendly environment, as well as provide appropriate orientation and stimulation to patients, especially those with baseline cognitive deficits.

Dehydration and electrolyte abnormalities should be corrected as quickly and safely as possible. Malnutrition should be corrected, unless there are good reasons not to (eg, terminal dementia).

Early correction of sleep disturbance, preferably by nonpharmacologic means, should occur, although the use of nonbenzodiazepine agents, such as melatonin or melatonin agonists (ie, ramelteon) or sedating antidepressant agents (eg, trazodone or mirtazapine) should be considered. On the other hand, clinicians must consider factors, such as drug–drug interaction and medication half-lives when prescribing. For example, mirtazapine and trazodone may indeed promote night sleep, but their effects may last well into the next day, interfering with cognition, attention, and concentration. Sedative agents with high anticholinergic load, such as antihistaminic agents (eg, diphenhydramine, hydroxizine) or tricyclic antidepressants (eg, amitriptyline) should be avoided, as they will aggravate delirium even if immediately effective in promoting sleep. Similarly, benzodiazepines should also be avoided if at all possible.

Finally, conduct an inventory of all pharmacologic agents being administered to the patient. Any medication or agent known to cause delirium (see Box 1) or to have high anticholinergic potential (see Box 2) should be discontinued, if possible, or a suitable alternative instituted.

Pharmacologic treatment strategies

It cannot be overstated that the definitive treatment of delirium is the accurate identification and treatment of its underlying causes. Nevertheless, pharmacologic intervention with various psychoactive agents is often needed to help manage agitated patients. Following the Hippocratic principle of "first, do no harm," clinicians should first avoid the use of GABAergic agents, if at all possible. As described above, all such agents (ie, benzodiazepines, propofol) may cause or aggravate delirium and its behavioral manifestations [20,41,94]. The use of benzodiazepines in the

management of delirium should be limited to: (a) patients experiencing delirium related to the withdrawal from a CNS-depressant agent (ie, alcohol, barbiturates, benzodiazepines); or (b) when other more appropriate agents (see below) have failed and the level of agitation and need for behavioral control outweighs the potential detrimental effects of benzodiazepines. Similarly, clinicians should do everything possible to avoid the use of opioid agents to tranquilize agitated patients, as opioids have been implicated in the development of delirium in many patient populations [25,40,101–106]. On the other hand, opioids should be administered when there is evidence that pain may be a contributor to the patient's agitation.

The literature has long recognized that intravenous neuroleptic agents are the recommended emergency treatment for agitated and mixed type delirium [164–169]. The intravenous administration of haloperidol has always been thought of as superior to oral administration because the IV route has more reliable absorption, even in cases of systemic organ failure. Intravenous haloperidol use has the added advantage of requiring no patient's cooperation, thus facilitating its use even in uncooperative and agitated patients. Studies suggest that the IV use of high-potency neuroleptic agents is associated with minimal effects on blood pressure, respiration, and heart rate [167,170–175].

Further research suggests a decreased incidence of extrapyramidal symptoms (EPS) when the intravenous route versus the oral route is used [176]. This study consisted of a retrospective chart review of all patients admitted to a large university hospital receiving haloperidol in any form over a 90-day period. A total of 238 subjects receiving haloperidol were identified during the index period, using data obtained through the digital pharmacy distribution system (Pyxis). Only patients with a known pre-existing movement disorder (eg, Parkinson disease) were excluded. In this sample, 51% of the subjects were women and the mean age was 62 years for women and 55 years for men. The most common reasons for which haloperidol was prescribed included delirium (69%), psychosis (11%), nausea or vomiting (9%), affective disorder (6%), and dementia (5%). Haloperidol doses ranged from 0.5 mg to 90 mg per day for subjects receiving intravenous administration, and from 0.5 mg to 20 mg per day for those receiving oral administration. Results show that patients receiving IV-haloperidol experienced much lower EPS than patients receiving the oral form (7.2% versus 22.6%; $P < .01$). In this sample, the most common forms of EPS observed included medication-induced Parkinsonism (50%), akathisia (32%), and acute dystonic reactions (14%). The investigators found no cases of significant respiratory depression or Torsade de Pointes (TdP) deemed to have been caused by haloperidol use. These findings are similar to those previously reported, also suggesting a lower incidence of EPS when haloperidol is administered intravenously [168].

Maldonado and Dhami [177] conducted a prospective study, involving all patients ($n = 225$) admitted to the critical care unit during a 6-month period.

Subjects were monitored throughout their hospital stay to assess the effectiveness of a protocol-based management of delirium among critical care patients. Subjects were followed daily by the study research assistant, using objective methods to assess delirium (ie, the MMSE [137] and the DRS [144]). There were slightly more surgical cases ($n = 129$), than medical cases ($n = 96$). A total of 18% of the subjects were identified as being delirious by DRS-criteria during the index period. Consultations to the Psychosomatic Medicine Service (PMS) were called in only 42% of the cases. On average, the surgical team consulted psychiatry 2.8 days after the onset of manifestation of delirium, whereas medicine services called after 4.2 days. Pharmacologic management varied significantly between the two groups (ie, standard of care versus study protocol). Medical and surgical services managed their delirious patients with varying combinations of medications, including opioids, benzodiazepines (ie, primarily midazolam or lorazepam), propofol, and various neuroleptic agents, usually on an as-needed basis. On the other hand, the treatment used by the PMS consisted of the routine use of IV haloperidol given throughout the day, on a regular schedule every 0400-, 1000-, 1600-, and 2200-hours. Lorazepam was used in cases of agitated delirium not responding to haloperidol alone, in cases of primary CNS-depressant agent withdrawal (ie, alcohol, benzodiazepines), or at night only to help promote sleep. The treatment regime doses were adjusted every 24 hours and titrated to effect. The dosing difference maintained a haloperidol-to-lorazepam ratio of at least two-to-one (the H2A protocol) to avoid the possibility of disinhibition by the benzodiazepines. That is, when used, the lorazepam dose was always less than half the haloperidol dose in milligrams. Nevertheless, because of the possibility that benzodiazepines themselves may contribute to delirium, the lowest effective dose was always used. Whenever possible, no benzodiazepines were used.

The results demonstrated that the PMS-management approach (ie, scheduled IV haloperidol use) was superior to the ''standard approach'' (ie, as-needed use of sedatives and antipsychotics) at treating delirium [177]. The length of stay (15 versus 11 days) (Fig. 7A), total duration of delirium (13 versus 6 days) (Fig. 7B), and percentage time being delirious (86% versus 58%) (Fig. 7C) were all shorter on patients treated by the PMS protocol. In addition, a significant improvement in cognitive functioning was observed in patients treated with the PMS-protocol. Finally, complete resolution of delirium (as measured by a MMSE greater than 26 and a DRS less than 10) at the time of discharge home was greater for patients treated with the PMS-protocol than (90% in the psychiatry group versus 14% in the medical/surgical group) (Fig. 7D). As many previous studies have indicated, these results suggest that a rational and controlled approach to the early identification and treatment of delirium in critical care patients results in a more accurate and prompt diagnosis, shorter hospital stays, a reduction in the use of restraints, faster recovery, and a substantially greater resolution of symptoms of delirium at the time of hospital discharge. Even though the

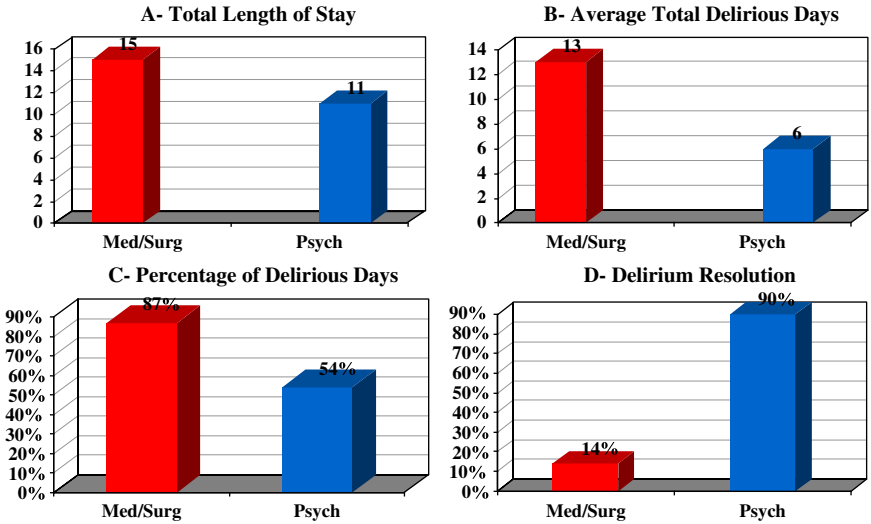

Fig. 7. Effects of the early identification and treatment of delirium according to protocol. (*A*) total length of stay; (*B*) average total delirious days; (*C*) percentage of delirious days. Final bar graph represents complete resolution; (*D*) percentage of complete resolution of delirium on discharge home by treatment groups. Red = treatment as usual by medical/surgical teams; Blue = psychological protocol treatment. (*From* Maldonado JR, Dhami N. "Recognition and Management of Delirium in the Medical and Surgical Intensive Care Wards." Poster presentation. 17th World Congress on Psychosomatic Medicine, Waikoloa, Hawaii. August 27, 2003; with permission; *Data from* Maldonado JR, Dhami N. Recognition and management of delirium in the medical and surgical intensive care wards. Journal of Psychosomatic Research 2003;55(2):150.)

number of patients treated by "standard or conventional" approach achieving a complete resolution of their symptoms of delirium appears dismal, these findings may represent more of the rule than the exception.

Levkoff and colleagues [120] followed all older patients ($n = 325$) admitted to the medical and surgical services of a teaching hospital. During the index period, 10.5% of all patients fulfilled DSM-III [178] criteria for delirium on admission and an additional 31.1% developed delirium during the index hospitalization. Similar to previous studies, development of delirium was associated with prolonged hospital stay and an increased risk of institutional placement among community-dwelling older persons. In their sample, only 4% of delirious patients in their study experienced full resolution of delirium symptoms before discharge from the hospital. On longitudinal follow-up, an additional 20.8% had resolution of all symptoms by 3 months, and an additional 17.7% had resolution of all symptoms by 6 months after discharge from the hospital.

Despite the widespread use of IV haloperidol and multiple reports in the literature describing its safety [166,167,169–172,174,175,179], even when used at fairly high doses, some reports suggesting a range of

500 mg–1,000 mg per day [172], fears about its use remain. The main concern when used in the acute care setting is related to it potential effect in prolonging QTc. There have been reports regarding the occurrence of QTc prolongation and even the development of TdP associated with haloperidol use. Nevertheless, the literature suggests that the risk is relatively low (0.27%) [180]. One of the problems in determining the exact contribution of IV haloperidol on TdP is that most patients for whom IV haloperidol is prescribed are very medically ill, usually in a critical care environment, and receiving multiple medications, many of which themselves could cause QTc prolongation and lead to TdP (Table 4) [181]. Justo and colleagues [182] conducted a review of published cases ($n = 70$) of TdP induced by psychotropic agents (PAs). They concluded that the most commonly identified risk factor for this patient population included female gender (50 of 70, 71.4%); advanced heart disease (24 of 70, 34.2%); hypokalemia; high doses of the offending agent (19 of 70, 27.1%); concomitant use of more than one PA, or another agent that might prolong the QT interval (21 of 70, 30%), and a history of long-QT syndrome (13 of 70, 18.5%) (Fig. 8). For

Table 4
Twenty drugs most commonly associated with Torsades de Pointes (TdP) according to adverse drug reactions (ADR) reported to world health organization, 1983–1999

Drug	TdP N[a]	Fatal N[b]	Total N[c]	TdP/total %
Sotalol	130	1	2,758	4.71
Cisapride	97	6	6,489	1.49
Amiodarone	47	1	13,725	0.34
Erythromycin	44	2	24,776	0.18
Ibutilide	43	1	173	24.86
Terfenadine	41	1	10,047	0.41
Quinidine	33	2	7,353	0.45
Clarithromycin	33	0	17,448	0.19
Haloperidol	21	6	15,431	0.14
Fluoxetine	20	1	70,929	0.03
Digoxin	19	0	18,925	0.10
Procainainide	19	0	5,867	0.32
Terodiltne	19	0	2,248	0.85
Fluconazole	17	0	5,613	0.30
Disopyramide	16	1	3,378	0.47
Bepridil	15	0	384	3.91
Furosemide	15	0	15,119	0.10
Thioridazine	12	0	6,565	0.18
Flecainide	11	2	3,747	0.29
Loratadine	11	1	5,452	0.20

[a] Total number of ADR reports that named TdP for this drug.
[b] Number of ADR reports that named TdP with fatal outcome.
[c] Total number of ADR reports for this drug.
Data from Vieweg WV. New Generation Antipsychotic Drugs and QTc Interval Prolongation. Primary care companion to the Journal of clinical psychiatry 2003;5(5):213.

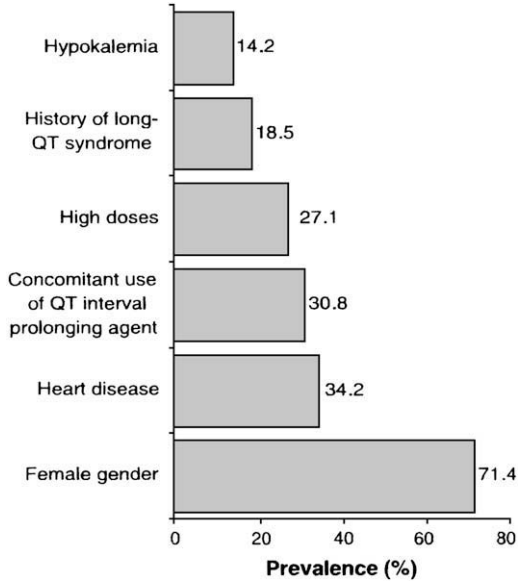

Fig. 8. Prevalence of risk factors for Torsade de Pointes among patients with TdP induced by psychotropic drugs. (*From* Justo D, Prohorov V, Heller K, et al. Torsade de Pointes induced by psychotropic drugs and the prevalence of its risk factors. Acta Psychiatr Scand 2005;111(3):171–6; with permission.)

a comprehensive review of medications that cause QTc prolongation and TdP, see Yap and Camm (Table 5) [183].

A MEDLINE and manual search of the literature published between 1966 and 1996 was conducted looking for cases of conduction disturbances associated with the use of butyrophenone antipsychotics [184]. They found only 18 patients described and concluded that, ''it seems reasonable to suggest that the incidence of adverse cardiovascular effects due to droperidol and haloperidol is small.'' The investigators made several recommendations regarding the use of haloperidol in the critically ill patient. Before initiating therapy with haloperidol, a baseline QTc interval and serum magnesium and potassium concentrations should be measured. Electrolytes should be corrected, if necessary, before initiation of treatment. If the baseline QTc interval is greater than or equal to 440 msec, and patients are receiving other drugs that may prolong the QTc interval or in the presence of significant electrolyte disturbances, a butyrophenone antipsychotic should be used with caution. Once treatment has been initiated, all critically ill patients receiving haloperidol should undergo regular electrocardiograph monitoring and QTc interval measurement. Special attention should be given to those receiving doses greater than 50 mg every 24 hours. Based on the currently available literature, any critically ill patient receiving droperidol or

Table 5
Drugs that can prolong QT interval and Torsades de Pointes (this list is not comprehensive)

Antiarrhythmic drugs	Type 1A (TdP reported in all)
	Quinidine (TdP reported)
	Procainamide (TdP reported)
	Disopyramide (TdP reported)
	Ajmaline (TdP reported)
	Type 1C (increase QT by prolonging QRS interval)
	Encainide
	Flecainide
	Type 3 (TdP reported in all)
	Amiodarone
	Sotalol
	d-Sotalol
	Bretylium
	Ibutilide
	Dofetilide
	Amakalant
	Semantilide
Calcium channel blockers	Prenylamine (TdP reported, withdrawn)
	Bepridil (TdP reported, withdrawn)
	Terodiline (TdP reported, withdrawn)
Psychiatric drugs	Thioridazine (TdP reported)
	Chlorpromazine (TdP reported)
	Haloperidol (TdP reported)
	Droperidol (TdP reported)
	Amitriptyline
	Nortriptyline
	Imipramine (TdP reported)
	Desipramine (TdP reported)
	Clomipramine
	Maprotiline (TdP reported)
	Doxepin (TdP reported)
	Lithium (TdP reported)
	Chloral hydrate
	Sertindole (TdP reported, withdrawn in the UK)
	Pimozide (TdP reported)
	Ziprasidone
Antihistamines	Terfenadine (TdP reported, withdrawn in the United States)
	Astemizole (TdP reported)
	Diphenhydramine (TdP reported)
	Hydroxyzine
	Ebastine
	Loratadine
	Mizolastine
Antimicrobial and antimalarial drugs	Erythromycin (TdP reported)
	Clarithromycin (TdP reported)
	Ketoconazole
	Pentamidine (TdP reported)
	Quinine
	Chloroquine (TdP reported)
	Halofantrine (TdP reported)

	Sparfloxacin
	Grepafloxacin (TdP reported, withdrawn in the UK and United States)
	Pentavalent antimonial meglumine
	Ketanserin (TdP reported)
Serotonin agents	Amantadine (TdP reported)
Promotility agents	Cisapride (TdP reported, withdrawn in the UK and United States)
Immunosuppressant	Tacrolimus (TdP reported)
Antidiuretic hormone	Vasopressin (TdP reported)
Other agents	Adenosine
	Organophosphates
	Probucol (TdP reported)
	Papaverine (TdP reported)
	Cocaine

Data from Yap YG, Camm AJ. Drug induced QT prolongation and Torsades de Pointes. Heart 2003;89(11):1367.

haloperidol therapy, whose QTc interval lengthens by greater than or equal to 25% over baseline, should undergo dose reduction or should be switched to a different agent.

Despite these concerns, in 1995 a task force of more than 40 experts in disciplines related to the use of analgesic and sedative agents in the ICU was convened from the membership of the American College of Critical Care Medicine and the Society of Critical Care Medicine (SCCM) [185]. This consensus of experts provided six recommendations with supporting data for intravenous analgesia and sedation in the ICU setting:

Morphine sulfate is the preferred analgesic agent for critically ill patients.
Fentanyl is the preferred analgesic agent for critically ill patients with hemodynamic instability, for patients manifesting symptoms of histamine release with morphine, or morphine allergy.
Hydromorphone can serve as an acceptable alternative to morphine.
Midazolam or propofol are the preferred agents only for the short-term (< 24 hours) treatment of anxiety in the critically ill adult.
Lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult.
Haloperidol is the preferred agent for the treatment of delirium in the critically ill adult.

Similarly, the use of IV haloperidol as the agent of choice for critically ill patients was reinforced by the SCCM's most recent guidelines, published in 2002 [186]. Since then, a "best evidence topic in cardiac surgery" was written according to a structured protocol, addressing the issue of haloperidol safety for critically ill patients. Their search included 294 articles and concluded that haloperidol should be considered the first-line drug for agitated patients after cardiac surgery [187].

Of note, in September 2007, the Food and Drug Administration (FDA) issued a ''black-box'' warning for the ''off-label'' clinical practice of using IV haloperidol [188]. It is important to remember that haloperidol has never been approved by the FDA for IV use.

Alternatives to haloperidol

Because of the stigma and potential side effects associated with typical antipsychotics, atypical agents (also known as second-generation antipsychotics, or SGA) have been used at increasing rates over the last few years for management of psychiatric symptoms (eg, agitation, psychosis, delirium) in medically ill patients. Large studies, particularly head-to-head comparison between SGA and more conventional agents (ie, haloperidol) are lacking. At least one study suggested that SGA may have a greater incidence of adverse effects than typical agents, excluding EPS [189]. Leucht and colleagues [190] conducted a meta-analysis of all randomized, controlled trials in which new generation antipsychotics (ie, SGA) had been compared with conventional drugs. The study included studies that met quality criteria A or B in the *Cochrane Collaboration Handbook*, and assessed quality with the Jadad scale. The investigators included in their analysis 31 studies with a total of 2,320 participants. The findings concluded that of the new generation drugs, only clozapine was associated with significantly fewer EPS (risk difference or RD = −0.15, 95% CI, −0.26 to −0.4, $P = .008$) and higher efficacy than low-potency conventional drugs. The reduced frequency of EPS seen with olanzapine was of borderline significance (RD = −0.15, CI, −0.31 to −0.01, $P = .07$). Similarly, they identified only one inconclusive trial of quetiapine and risperidone, and no investigations of ziprasidone and sertindole. They concluded that as a group, new generation drugs were moderately more efficacious than low-potency antipsychotics, largely irrespective of the comparator doses used; and that optimum doses of low-potency conventional antipsychotics might not induce more EPS than new generation drugs.

Other problems to consider when choosing an alternative agent include the fact that SGA may be associated with weight gain, dyslipidemia, high blood pressure, and ultimately with cardiovascular disease, diabetes, and metabolic syndrome [191]. As when considering the use of typical agents (ie, haloperidol), clinicians must consider these factors and weigh potential risks and benefits before prescribing these agents to a critically ill patient. Finally, there is also evidence that some atypical agents may aggravate or cause delirium (eg, clozapine, olanzepine), probably because of their anticholinergic potential [189]. Data on most atypical agents are limited to small case reports.

Horikawa and colleagues [192] conducted a prospective open trial on risperidone for the treatment of delirium among medically ill patients ($n = 10$). They reported an overall effectiveness of 80%, using doses of risperidone between 0.5 mg to 2 mg per day. Side effects included sedation in 30%

and EPS in 10% of subjects. Mittal and colleagues [193] reported similar results ($n = 10$) with risperidone, using a mean daily dose of 0.75 mg. The largest, open-label risperidone study was reported by Parellada and colleagues [194], who followed subjects hospitalized for a medical condition ($n = 64$). Once the diagnosis of delirium was established (based on the DRS) treatment with risperidone was initiated. The investigators reported improvements on all studied measures (ie, Clinical Global Impressions or CGI scale, DRS, and MMSE) after 7 days of treatment. There was a very low incidence of overall adverse effects (3.1%) and no EPS reported. On the other hand, there are at least four publications reporting risperidone-induced delirium [195–198].

There are six publications reporting on the use of quetiapine for the treatment of delirium. Torres and colleagues [199] reported improvements on MMSE and DRS-R-98 in two subjects. Similarly, Al-Samarrai and colleagues [200] reported on another two delirious subjects responding to quetiapine. Sasaki and colleagues [201] reported on a prospective, open-label study ($n = 12$) of delirious subjects treated with a mean daily dose of quetiapine of 45 mg plus or minus 31 mg per day. They found a mean duration of symptoms of 4.8 plus or minus 3.5 days and improvements on MMSE, and reported no significant side effects. Similarly, Kim and colleagues [202] reported on another 12 subjects treated with a mean daily dose of quetiapine of 94 mg plus or minus 23 mg per day. The mean duration of symptoms was 5.9 plus or minus 2.2 days, as well as improvements on the clock drawing test and MMSE. Pae and colleagues [203] treated 22 subjects with a mean daily dose of quetiapine of 127.1 mg plus or minus 72.2 mg per day. In this group, the mean duration of symptoms was 8.5 plus or minus 4.5 days, as well as improvements on DRS-R-98 and CGI. Again, no significant side effects were reported. Maneeton and colleagues [204] studied the effectiveness of quetiapine in the management of delirium ($n = 22$) in an open-label study. The means (SDs) dose and duration (SD) of quetiapine treatment were 45.7 (28.7) mg per day and 6.5 (2.0) days, respectively. Results show that the DRS and CGI-S scores of days two to seven were significantly lower than those of day 0 ($P < .001$) for all comparisons. The incidence of side effects was minimal. Finally, Balit and colleagues [205] and Sim and colleagues [206] reported on a case each in which quetiapine was the suspected cause of delirium.

There are several publications reporting the use of olanzapine for the treatment of delirium. Kim and colleagues [207] reported on an open trial ($n = 20$) on the use of olanzapine for the treatment of delirium caused by multiple medico-surgical conditions. The average olanzapine dose was 5.9 mg plus or minus 1.5 mg per day and the average duration of treatment was 6.6 plus or minus 1.7 days. Their data showed improvement in the DRS at relatively low doses (5.9 mg $\pm$ 1.5 mg per day) and no evidence of significant side effects. Passik and Cooper [208] and Halil and colleagues [209] reported a single case report each in which olanzepine was successfully used in the treatment of delirium associated to a medical problem. Breitbart

and colleagues [210] conducted an open, prospective trial of olanzapine for the treatment of delirium in hospitalized cancer patients ($n = 79$). In this sample, olanzepine was effective in treating 76% of delirium patients as evidenced by the Memorial Delirium Assessment Scale (MDAS) [211], but recorded problems with excessive sedation in 30% of patients. They also described several factors significantly associated with poorer response to olanzapine treatment for delirium, including age greater than 70 years, history of dementia, central nervous system spread of cancer and hypoxia as delirium etiologies, hypoactive delirium, and delirium of "severe" intensity (as measured by an MDAS greater than 23). Robinson and colleagues [212], Steil [213], Morita and colleagues [214], Samuels and Fang [215], Prommer [216], Arora and Praharaj [217], and Lim and colleagues [218] all reported on cases associated with olanzapine-induced delirium at therapeutic doses. Delirium has been reported as a side effect in 54% of the cases when large doses of olanzepine have been ingested in an overdose. Patients with olanzapine-induced delirium had an increased length of hospital stay and ICU admission rate (50%), and 70% of them required physical or chemical restraint [219].

Aripiprazole has been described as an effective treatment of delirium in two case reports [220]. Straker and colleagues [221] reported on an open-label series of subjects ($n = 14$) treated with aripiprazole for management of delirium used in a flexible dosing range, from 5 mg per day to 15 mg per day, titrated over a 7-day period, with dose increases on day 3 and day 7, as clinically indicated. DRS-R-98 scores declined from 25.1 ($\pm$5.2) on initial evaluation to 9.4 (4.9) at treatment end-point. Fifty percent of the subjects (7 out of 14) had improved significantly (ie, $\geq$ 50% reduction in DRS-R-98 scores) by day 5, while 12 of the 14 subjects had a reduction in their DRS-R-98 scores greater than or equal to 50% by treatment end-point.

To date, there are two single case reports on the use of ziprasidone for the management of delirium [222,223]. There is at least one open-label study ($n = 38$) on the use of perospirone, a recently developed atypical antipsychotic with potent serotonin 5-HT2 and dopamine D2 antagonist activity. Perospirone was effective in 86.8% of patients (based on DRS-98 assessments) and the effect appeared within several days (5.1 $\pm$ 4.9 days). The initial dose was 6.5 mg plus or minus 3.7 mg per day and maximum dose of perospirone was 10.0 mg plus or minus 5.3 mg per day. Reported side effects included fatigue (15.2%), sleepiness (6.1%), akathisia (3.0%), and hypotension (3.0%) [224].

There is little published data regarding controlled studies of atypical antipsychotics for the treatment of delirium. Sipahimalani and Masand [225] conducted a single-blind study using olanzepine versus haloperidol. Eleven subjects with delirium were treated, using a mean daily dose of olanzepine of 8.2 mg plus or minus 3.4 mg versus haloperidol 5.1 mg plus or minus 3.5 mg per day. Peak response (ie, the number of days the patient received the neuroleptic before achieving maximum improvement) was similar in both groups (mean $\pm$ SD: 6.8 $\pm$ 3.5 days for olanzapine and

7.2 ± 4.9 days for haloperidol, $P = .8279$). Mean plus or minus SD pretreatment DRS scores were comparable in the olanzepine (17.9 ± 4.4) and the haloperidol (20.1 ± 5.2) groups ($P = .2968$). Mean plus or minus SD after-treatment DRS scores were 10.3 plus or minus 4.8 for the olanzapine group and 11.1 plus or minus 7.1 for the haloperidol group ($P = .7601$). The mean improvement was 7.6 for the olanzapine group and 10 for the haloperidol group. Five of the olanzapine subjects and six of the haloperidol subjects showed a greater than 50% reduction in their DRS scores.

Schwartz and Masand [226] performed a single-blind study of quetiapine versus haloperidol in delirious subjects ($n = 11$). The quetiapine average daily dose was 200 mg per day. The investigators reported an effectiveness of greater than or equal to 50% in reducing DRS scores. When compared with haloperidol, there was no difference in onset of symptom resolution, duration of treatment, and overall clinical improvement. Skrobik and colleagues [227] conducted an open-label, prospective randomized trial, comparing the use of enteral olanzepine (dosed at 5 mg per day) or haloperidol (dosed at 2.5 mg–5 mg every 8 hours) in the treatment of delirium in a critical care setting. Delirium Index decreased over time in both groups, as did the administered dose of benzodiazepines. Clinical improvement was similar in both treatment arms. The dose of rescue haloperidol, opiates, sedatives other than benzodiazepines, Ramsay scores, vital signs, and liver function tests were no different between groups. Thus, no significant clinically effective difference was appreciated between groups. Liu and colleagues [228] conducted a single-blind risperidone versus haloperidol study. They treated 41 subjects with a mean daily dose of risperidone of 1.2 mg plus or minus 0.75 mg per day. The investigators found no significant difference in the efficacy or frequency of response rate between haloperidol and risperidone on any of the measures (ie, DRS, MDAS).

The only published double-blind, randomized study looked at 28 subjects with delirium who were randomly assigned to receive a flexible-dose regimen of haloperidol or risperidone over a 7-day treatment period [229]. The severity of delirium was assessed by using the MDAS and the DRS. The study investigators found no significant difference in the efficacy, frequency, or rate of response between haloperidol and risperidone on any of the measures. Similarly, there were no clinically significant side effect differences among study groups.

A Cochrane Database review study looking at the use antipsychotics for the treatment of delirium was conducted and included haloperidol and all atypical antipsychotics for which data has been published [230]. Only three studies met the design criteria. These compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and the incidence of adverse drug reactions. The authors concluded that the decreases in delirium scores were not significantly different comparing the effect of low dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (OR 0.63; 95% CI, 10.29–1.38; $P = .25$), and that low-dose haloperidol did not have a higher incidence of adverse effects

than the atypical antipsychotics. Finally, low-dose haloperidol may be effective in decreasing the degree and duration of delirium in postoperative patients, compared with placebo.

Ozbolt and colleagues [231] conducted a search of the published literature on atypical antipsychotic agents for the treatment of delirium using MEDLINE and PubMed for articles (including review articles, randomized controlled trials, clinical trials, or meta-analyses) written in English. They found that risperidone was the most thoroughly studied atypical antipsychotic for the management of delirium. In most studies, risperidone was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at doses of 0.5 mg to 4 mg per day. The search indicates that olanzapine was approximately 70% to 76% effective in treating the behavioral manifestations of delirium at doses of 2.5 mg to 11.6 mg per day. There were very few studies conducted using quetiapine, although available data suggests that it also appears to be a safe and effective alternative to high-potency antipsychotics. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects.

Antipsychotics are widely used to manage behavioral disorders, including delirium, in patients with dementia. Recently, serious concerns have been raised about the stroke and mortality risk of atypical antipsychotics when administered to patients with dementia. Schneider and colleagues [232] reviewed 15 clinical trials, including 16 contrasts of atypical antipsychotic drugs with placebo (aripiprazole [$n = 3$], olanzapine [$n = 5$], quetiapine [$n = 3$], risperidone [$n = 5$]) and a total of 3,353 subjects randomized to study drug versus 1,757 randomized to placebo. The investigators found that death occurred more often among patients randomized to drugs (118 or 3.5% versus 40 or 2.3%; the OR by meta-analysis was 1.54; 95% CI, 1.06–2.23; $P = .02$; RD 0.01; 95% CI, 0.004–0.02; $P = .01$). The results suggested that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo.

Yet, an even more recent study by Raivio and colleagues [233] examined the use of antipsychotic agents to manage behavioral disorders in patients ($n = 254$) with dementia. In this sample, nearly half (48.4%) of the patients were administered antipsychotic medication. A total of 37.4% received conventional neuroleptics ($n = 95$), while only 11.0% received atypical antipsychotics ($n = 28$). The mean number of hospital admissions was higher among the non-users than among the users of conventional or atypical antipsychotics. Among the users of atypical antipsychotics (eg, risperidone, olanzapine), 32.1% died within 2 years, compared with 45.3% in the conventional neuroleptics group, and 49.6% in the non-neuroleptic user group. In the Cox proportional hazard model, a high number of medications and the use of physical restraint predicted higher mortality at 2 years. On the other hand, the use of atypical antipsychotics showed lower risk of mortality, if any. The investigators concluded that neither the use of atypical

antipsychotics, nor the use of conventional neuroleptics increased mortality or hospital admissions.

One study pooled QTc interval data from acutely agitated patients across four double-blind trials and showed that when all of the intramuscular olanzapine data were considered, QTc interval changes were small, variable, and generally symmetric at around 0, suggesting that these values were reflective of normal and random intra-individual variability [234]. A series of case reports by Balit and colleagues [205] implicated that quetiapine poisoning was associated with an increase in the mean QTc interval. The FDA has published data on the effect of atypical antipsychotics on QTc interval (Table 6). Yet, no new generation antipsychotic drug has been associated with Torsade de Pointes. All of them have been associated with QTc interval prolongation. In order of degree, QTc interval prolongation is greatest with ziprasidone and least with olanzepine [235].

Finally, one must consider the fact that newer antipsychotic agents (SGA) have a wider range of pharmacologic affinity (ie, affects a greater number of neurotransmitters and receptors) than older agents. Although SGA may have lower EPS side effects, they have other undesirable side effects, such as high sedation and anticholinergic activity (Fig. 9). The sedative effect may be considered desirable in the case of agitated agents, although given the agents relatively long half-lives this may later affect attention and cognition and be detrimental in cases of hypoactive delirium. On the other hand, anticholinergic side effects are never desirable when it comes to delirium and this may be a consideration when making treatment choices.

Nonantipsychotic agents

Addressing the theory that proposes delirium is caused by a central cholinergic deficiency state, some researchers and clinicians have experimented with the use acetylcholinesterase inhibitor agents. Most of the published data consists of small series of case reports associated with the use of rivastigmine in the treatment of delirium in older persons [236,237]. There have been at least 19 articles, mostly case reports, suggesting that

Table 6
Effects of orally-administered antipsychotics on the QT interval

Drug	Mean increase in QTc (ms)	% of subjects with > 60 ms increase in QTc
Thioridazine	35.8	29
Ziprasidone	20.6	21
Quetiapine	14.5	11
Risperidone	10.0	4
Olanzapine	6.4	4
Haloperidol	4.7	4

Data from Huffman JC, Stern TA. QTc Prolongation and the use of antipsychotics: A case discussion. Primary Care Companion to the Journal of Clinical Psychiatry 2003;5(6):278–81.

Binding of atypical antipsychotics at dopamine 2 (D2) and muscarinic receptors (MR)[a]

Medication	D2[b]	MR[b]	D2/MR	MR1[c]	MR2[c]	MR3[c]	MR4[c]	MR5[c]
Aripiprazole	0.45[d]	>10, 000[d]	<0.0001	6780[e]	3510[e]	4680[e]	1520[e]	2330[e]
Clozapine	210	9	23.3	1.4	10	7	6	5
Olanzapine	20	36	0.56	2.5	18	13	10	6
Quetiapine	770	1400	0.55	120	630	1320	660	2990
Risperidone	3.77	34, 000	0.0001	>10,000	>10,000	>10,000	>10,000	>10,000
Ziprasidone	2.6	2440	0.001	5100[f]	>3000	>1300	>1600	>1600

[a] Values reported are either equilibrium dissociation (K_d) or inhibitory (K_i) constants in nanomolar (nM) units. Both constants reflect affinity; smaller values indicate greater receptor affinity.
[b] Used human brain (caudate nucleus) homogenate in buffer with [^{3}H]-spiperone for D2 and [^{3}H]-QNB for MRs (Richelson and Souder, 2000).
[c] Used clonal cell membranes in buffer with [^{3}H] *N*-methylscopolamine (Bymaster et al., 1996; Bymaster and Falcone, 2000; Bymaster et al., 2003a).
[d] Specific details regarding the source of receptors and the radioligands used were not provided (Briston-Myers Squibb, data on file; Goodnick and Jerry, 2002).
[e] Used clonal cell membranes in buffer with [^{3}H]-QNB (Shapiro et al., 2003).
[f] Used clonal cell membranes with [^{3}H] *N*-methylscopolamine (Schmidt et al., 2001). Please note, Bymaster and colleagues (2003a) reported the binding affinity of ziprasidone at MR1 to be 300 nM.

Fig. 9. Binding of atypical antipsychotics at dopamine 2 (D2) and muscarinic receptors (MR).[a]

acetylcholinesterase inhibitor agents (eg, donepezil, galantamine, physostigmine, rivastigmine) may be effective in the treatment of delirium (Box 6).

Some have theorized that an impaired serotonin metabolism may play a role in the development of delirium. At least one report suggests that the antiemetic agent ondansetron (ie, a selective serotonin 5-HT_3-type receptor antagonist) may be effective in the treatment of delirium. Bayindir and colleagues [238] conducted a prospective study of patients ($n = 35$) who developed delirium in the intensive care unit after coronary artery bypass graft surgery. The investigators developed a behavioral scoring scale, with

Box 6. Case reports suggesting a positive effect of acetylcholinesterase inhibitors in the treatment of delirium

Burt 2000 [281]
Bruera, et al 2003 [282]
Dautzenberg, et al 2004 [236]
Fisher, et al 2001 [283]
Gleason 2003 [284]
Hasse and Rundshagen 2007 [285]
Hori, et al 2003 [286]
Kaufer, et al 1998 [287]
Kobayashi, et al 2004 [82]
Logan and Stewart 2007 [288]
Moretti, et al 2007 [266]
Palmer 2004 [289]
Rabinowitz 2002 [290]
Weizberg, et al 2006 [291]
Wengel, et al 1998 [292]
Wengel, et al 1999 [293]

normal scored as 0, and severe verbal and physical agitation was scored as 4. After a subject was determined to be delirious, patients received a single IV dose of ondansetron (ie, 8 mg), and were re-evaluated 10 minutes later. Before the treatment, 7 subjects had a score of 2 (20%); 10 subjects had a score of 3 (28.6%); and 18 subjects had a score of 4 (51.4%). After the treatment, 28 subjects (80%) dropped their score to 0; 6 subjects (17.1%) dropped to a score of 1, and 1 subject (2.9%) remained at a score of 4. The mean score dropped from 3.20 plus or minus 1.01 to 0.29 plus or minus 0.75 after treatment. No adverse side effects were reported.

What about the treatment of hypoactive delirium?

This is a difficult aspect to discuss, as there is no available literature to guide us. As discussed above, most of these cases are unrecognized or misdiagnosed as depression. In either case, lack of recognition and treatment leads to the same poor outcomes previously described. Therefore, vigilance and screening, particularly in high-risk populations is imperative. Early intervention by specialized clinicians (eg, Psychosomatic Medicine Service or Geropsychiatric Service) has been shown to improve outcomes. Overall, several clinical principles apply: (1) prevention is key (see next section); (2) all other factors described above under nonpharmacologic approaches apply; (3) if pharmacologic agents are to be used, consider the least sedating available agents, such as haloperidol (for typical) or risperidone (for atypical). Furthermore, take into consideration the anticholinergic potential of the antipsychotic agent use (see Fig. 9). There may be reasons to consider use of nonantipsychotic agents (as described in the section above) to accelerate the rate of recovery and prevent further deterioration of cognitive status, but good controlled studies are lacking. Similarly, given the mechanism of delirium development, there may be a rationale for the use of very low doses of nonsedating antipsychotic agents (see the article by Maldonado titled, A Comprehensive Multifoactorial Understanding of the Neurobiology of Delirium and an Evidence-based Approach to Prevention & Treatment, elsewhere in this issue). Similarly, the use of activating agents (eg, modafinil and psychostimulants) may help mobilize hypoactive patients, particularly to address extreme psychomotor retardation and extreme somnolence once all potential contributing pharmacologic agents (eg, sedatives, opioids) have been removed.

Prevention of delirium

As described above, there are many risks factors for the development of delirium. Controlling for some of these may better assist on delirium prevention. The majority of patients in the ICU, particularly those who are mechanically ventilated, receive some form of sedation to reduce anxiety, encourage sleep, and to increase tolerance to the critical care environment,

including multiple lines, pain management, endotracheal tubes, and ventilators. Sedative and analgesic drugs are among the most commonly prescribed medications in the ICU [239]. As discussed above (see etiology section), sedative agents (mostly GABAergic) and opioids may contribute to the development of delirium by one of five mechanisms: (1) interfering with physiologic sleep patterns; (2) interfering with central cholinergic function; (3) increasing compensatory up-regulation of N-methyl D-aspartate and kainite receptors and Ca2+ channels; (4) disrupting the circadian rhythm of melatonin release; and (5) disrupting thalamic gating function. To try to prevent delirium altogether, Maldonado and colleagues [240] were the first to report on the use of novel agents as alternative sedation in order minimize delirium by avoid the use of benzodiazepines and related agents (eg, midazolam, propofol) during the postoperative state. Postcardiotomy patients were selected, given the high incidence of delirium in postcardiotomy patients (around 57%) nationwide [26].

In the final analysis, Maldonado and colleagues [241] studied patients ($n = 118$) undergoing cardiac surgery (ie, repair or replacement) with CPB. Intraoperative anesthesia for the surgical procedures was standardized for all subjects. All procedures were performed via median sternotomy in conjunction with CPB and induction of moderate hypothermia. After successful weaning from CPB, subjects were started on one of three randomly assigned, postoperative sedation regimens: dexmedetomidine, propofol, or midazolam. Upon arrival at the ICU, a standardized protocol for postoperative care was implemented for all subjects. Study results show there were no significant preoperative or intraoperative differences between treatment groups (eg, age, sex, American Society of Anesthesiologists classes, bypass time, clamp time, or lowest temperature achieved). The only real difference in management between groups was the type of postoperative sedation. Final results demonstrated an incidence of delirium of 3% (1 out of 30) for subjects on dexmedetomidine, 50% (15 out of 30) for propofol, and 50% (15 out of 30) for midazolam ($P < .01$) (Fig. 10). The absolute risk reduction in the incidence of delirium associated with using dexmedetomidine was 47% (95% CI, 28%–66%) corresponding to an NTT (number needed to treat) of 2.1 subjects (95% CI, 1.5–3.6). As in other studies, subjects who developed postoperative delirium experienced significantly longer intensive care stays (4.1 versus 1.9 days, $P < .001$) and longer total hospitalization (10.0 versus 7.1 days, $P < .001$) compared with subjects without delirium. The average age of subjects who developed delirium was significantly older than those who did not (64.9 ± 15.9 versus 52.9 ± 16.1 years, $P < .001$) (Table 7).

Even though previous reports have suggested that the cognitive decline observed after cardiac surgery could be attributed to the use of the CPB pump [110,242,243], Van Dijk and colleagues [244] found no difference in cognitive outcomes in cardiac patients operated with the aid of CPB and without (off-pump), suggesting that factors other than CPB may be responsible for cognitive decline after cardiac surgery. Maldonado and

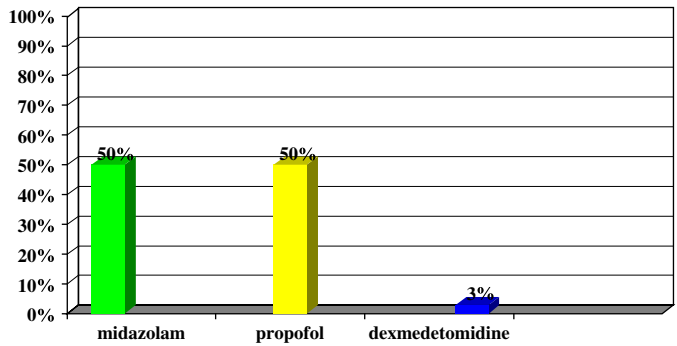

Fig. 10. Dexmedetomidine prophylaxis in postsurgical valve disease patients versus dexmedetomidine. $P < .01$, adjusted for comparing multiple group means. (*From* Maldonado J, Wysong A, van der Starre PJA, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Accepted for publication. Psychosomatics. 2008; with permission. Copyright © 2008, American Psychiatric Association.)

colleagues [241] study results support this theory, and suggest that postoperative sedation, not the CPB, is an independent negative factor for mental status changes (ie, delirium) in cardiac surgery patients.

The investigators proposed at least two sets of theories used to explain the fact that patients in the dexmedetomidine group experienced a lower incidence of postoperative delirium [241]. The first theory suggests that dexmedetomidine has intrinsic "delirium-sparing effects." Several specific characteristics of the drug may account for this effect. First, studies have suggested that the likelihood of delirium is increased with the number of neurotransmitter pathays disrupted [245–247]. Dexmedetomidine asserts its sedative effects by blocking a single neurotransmitter, norepinephrine, via αB_{2B}-adrenoceptor binding. The second characteristic is its effect in presynaptic noradrenergic transmission. Changes in the noradrenergic system have been described as potential causative factors in delirium, with increased levels of plasma free-MHPG (3-methoxy-4-hydrophenylglycol) concentration observed in some delirious states [246,248]. Third, dexmedetomidine produces sedation without respiratory depression [249]. Studies have demonstrated that hypoxia and anoxia in the central nervous system are critical events leading to the biomolecular derangements in delirium [245,250], while others [66] have reported lower postoperative oxygen saturation in postthoracotomy patients who developed delirium, compared with patients who did not develop delirium with the resolution of mental status changes after oxygen supplementation. Fourth, dexmedetomidine lacks clinically significant anticholinergic effects and, in fact, has some mild cholinergic activation [251]. A strong association has been documented between medications with anticholinergic potential and the development of delirium [86,88,90]. Fifth, several studies have suggested that postoperative sedation with dexmedetomidine has been associated with lower opioid requirements, an average of

Table 7
Selected postoperative outcome variables for cardiac patients with cardiopulmonary bypass by intervention group

	Dexmedetomidine ($n = 30$)	Propofol ($n = 30$)	Midazolam ($n = 30$)	overall p-value	Dex versus propofol	Dex versus midazolam
Delirium						
Incidence of delirium (per protocol)	1/30 (3%)	15/30 (50%)	15/30 (50%)	<0.001	<0.001	<0.001
Incidence of delirium (ITT)	4/40 (10%)	16/36 (44%)	17/40 (44%)	<0.001	0.001	0.002
Number of days delirious	2/216 (1%)	45/276 (16%)	75/259 (29%)	<0.001	<0.001	<0.001
Average length of delirium P[a](days)	2.0 ± 0	3.0 ± 3.1	5.4 ± 6.6	0.82	0.93	0.63
Time variables						
ICU length of stay (days)	1.9 ± .9	3.0 ± 2.0	3.0 ± 3.0	0.11	0.14	0.14
Hospital length of stay (days)	7.1 ± 1.9	8.2 ± 3.8	8.9 ± 4.7	0.39	0.42	0.12
Intubation time (hours)	11.9 ± 4.5	11.1 ± 4.6	12.7 ± 8.5	0.64	0.91	0.34
As needed medications						
Fentanyl (mcg)	320 ± 355	364 ± 320	1,088 ± 832	<0.001	0.93	<0.001
Total morphine equivalents (mg)P[b]	50.3 ± 38	51.6 ± 36	122.5 ± 84	<0.001	0.99	<0.001
Antiemetic use[c]	15/30 (50%)	17/30 (57%)	19/30 (63%)	0.58		
As needed medications for the management of delirium[d]						
Lorazepam	1/30 (3%)	7/30 (23%)	6/30 (20%)	0.07	0.06	0.11
Haloperidol	0/30	3/30 (10%)	2/30 (7%)	0.23	0.07	0.15

[a] Of patients who developed delirium.
[b] Sum of average morphine equivalents (fentanyl, oxycodone, and hydrocodone) received in postoperative days 1 to 3.
[c] Number of patients who received dolasetron mesylate or promethazine HCl in postoperative day 1.
[d] Average amount over 3 days. None of these medications were given until a diagnosis of delirium was established.

Data from Maldonado J, Wysong A, van der Starre PJA, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Accepted for publication, Psychosomatics 2008, in press; with permission.

40% lower [252,253]. This is significant, as studies have demonstrated a direct relationship between opiate use and development of delirium [254,255]. Sixth, dexmedetomidine is believed to promote a more physiologic sleep-wake cycle in the ICU setting [249,256]. This is important, as sleep deprivation and disruption have been implicated in the onset and perpetuation of delirium [166]. Finally, dexmedetomidine has been shown to have neuroprotective effects [257] in animal models of ischemia [258] and in human beings undergoing cardiac surgery [259].

The second theory suggests that the reason subjects had significantly less delirium in the dexmedetomidine group was not because of its use per se, but because those subjects were not exposed to other sedative agents with much greater delirium potential. As suggested by many others, GABAergic agents (ie, propofol, midazolam) have been implicated in the development of delirium. In fact, GABAergic medications and narcotics are among the factors associated with the onset and worsening of delirium [20,41,95,96], by interfering with physiologic sleep patterns and causing a centrally mediated acetylcholine deficient state, via interruption of central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus [95,97,245]. These may be mechanisms by which midazolam or propofol may contribute to higher rates of delirium [41,96]. Midazolam and propofol were specifically chosen as comparators, given these agents are customarily used in routine medical practice throughout critical and intensive care settings, and are both commonly used for postoperative sedation after cardiac surgery.

Antipsychotic agents for prevention of delirium

Antipsychotic agents have long been used for the treatment of the behavioral symptoms of delirium. Some suspect that they could be used to prevent delirium as well. At least one randomized, controlled trial addressed the issue of prophylactic haloperidol. In at-risk patients aged greater than 70 years, oral haloperidol 0.5 mg twice a day was administered from up to 72 hours preoperatively until the third postoperative day. The study found that prophylactic haloperidol use did not alter the incidence of postoperative delirium (15.1%) compared with placebo (16.5%; relative risk or RR 0.91; 95% CI, 0.59–1.44) [260].

On the other hand, in another study, elderly patients ($n = 430$) undergoing hip surgery were given 1.5-mg haloperidol per day or placebo, started preoperatively and continued for up to 3 days postoperatively [261]. Neuropsychiatric evaluations demonstrated that the overall incidence of postoperative delirium was 15.8%, but that subjects in the haloperidol group had a slightly lower incidence compared with placebo (15.1% versus 16.5%) (RR 0.91, 95% CI, 0.6–1.3); the mean highest DRS-R-98 score plus or minus SD was 14.4 plus or minus 3.4 and 18.4 plus or minus 4.3, respectively (mean difference 4.0, 95% CI, 2.0–5.8; $P < .001$); delirium duration was 5.4 versus 11.8 days, respectively (mean difference 6.4 days, 95% CI,

4.0–8.0; $P < .001$); and the mean number of days in the hospital was 17.1 plus or minus 11.1 and 22.6 plus or minus 16.7, respectively (mean difference 5.5 days, 95% CI, 1.4–2.3; $P < .001$). No haloperidol-related side effects were noted. Thus, the study suggests that although prophylactic treatment with low-dose haloperidol had no efficacy in reducing the incidence of postoperative delirium, it did have a positive effect on the severity and duration of delirium and shortened the length of hospital stay.

Prakanrattana and Prapaitrakool [262] conducted a randomized, double-blinded, placebo controlled trial ($n = 126$) of patients undergoing cardiac surgery with CPB. Subjects were randomly assigned to receive either 1-mg risperidone or placebo sublingually when they regained consciousness (ie, immediately after surgery). They found that the incidence of postoperative delirium in the risperidone group was lower than the placebo group (11.1% versus 31.7% respectively, $P = .009$, RR 0.35, 95% CI, 0.16–0.77). A recently presented abstract reported a significant decreased in the incidence of postoperative delirium following orthopedic joint replacement surgery ($n = 400$). The study compared olanzepine (5-mg Zydis formulation, administered just preoperatively, and 5 mg administered immediately after surgery upon awakening) to placebo. Researchers found the incidence of delirium in the intervention group was 15%, compared with 41% in the placebo-controlled group ($P < .0001$) [263].

Acetylcholinesterase inhibitors in delirium prevention

Despite the logical premise behind the prophylactic use of acetylcholinesterase inhibitor agents, two studies have failed to demonstrate efficacy in the prevention of postoperative delirium. The first study was a randomized, double-blind, placebo-controlled trial involving elderly patients undergoing elective total joint replacement surgery ($n = 80$) [264]. Each participant was evaluated before surgery and then received donepezil or placebo for 14 days before surgery and 14 days afterward. Delirium, diagnosed by DSM-IV criteria, was found in 18.8% of subjects, but there were no significant differences between the donepezil and placebo groups. Subsyndromal delirium was found in 68.8% of subjects, but again, there was no difference between groups.

A second study also failed to demonstrate efficacy of donepezil in preventing postoperative delirium after elective total hip replacement surgery in older people without pre-existing dementia ($n = 33$) [265]. The investigators randomized (double-blind, placebo controlled) subjects to receive either placebo or donepezil (5 mg) immediately postoperatively and every 24 hours thereafter for the first 3 postoperative days, with no serious adverse events reported. The overall incidence of postoperative delirium was 21.2% in all subjects, but there was no significant difference between the groups. The unadjusted risk ratio (donepezil versus placebo) for delirium was 0.29 (95% CI, 0.06, 1.30). The mean length of hospital stay was 9.9 days for

the donepezil group versus 12.1 days in the placebo group; difference in means equals −2.2 days (95% CI, −0.39, 4.78).

There have been some positive trials involving other agents. A study of dementia patients ($n = 366$) demonstrated that the chronic rivastigmine (a slowly reversible inhibitor of acetylcholinesterase and butyrylcholinesterase) group had a much lower incidence of delirium (45.5%), compared with the control group (88.9%) ($P < .05$) [236]. Another study has also demonstrated a decrease in the occurrence and duration of delirium in elderly patients ($n = 246$) suffering from vascular dementia [266]. Subjects were divided into two homogenous groups (matched for age and education levels): Group A received 3-mg to 6-mg rivastigmine per day, while Group B received 100-mg cardioaspirin per day. Both groups presented episodes of delirium, which occurred during a concomitant medical illness. During the follow-up period, the incidence of delirium was 40% in Group A versus 62% in group B ($P < .001$). Moreover, the mean duration of the delirium was shorter in Group A (mean duration 4 ± 1.71 days) compared with Group B (7.86 ± 2.73 days; $P < .01$).

Other pharmacologic agents as prevention strategies

A randomized, double-blind study involving children ($n = 85$) undergoing dental repair studied the effectiveness of ketamine (versus placebo) for the prevention of delirium in sevoflurane-induced anesthesia using the Pediatric Anesthesia Emergence Delirium scale. The study demonstrated a substantially lower incidence of emergence agitation in the ketamine group (16.6%) compared with the placebo group (34.2%). There was no difference in time to meet recovery room discharge criteria between the two groups [267].

Nonpharmacologic prevention strategies

Still, not all proposed prophylactic methods are pharmacologic. Inouye and colleagues [166] conducted a landmark study of hospitalized patients ($n = 852$) and assessed for manifestations of delirium in response to the correction of environmental factors commonly associated with increased risk for delirium. The intervention consisted of simple techniques applied by the hospital staff, including reorientation, appropriate cognitive stimulation three times a day, the implementation of a nonpharmacologic sleep protocol to help normalize a patient's sleep-wake cycle, early mobilization after surgery or extubation, timely removal of catheters and restraints, correction of sensory deficiencies (ie, eyeglasses and hearing aids), and early correction of dehydration and electrolyte abnormalities. As a result to these environmental manipulations, they observed an astonishing 40% reduction in odds for delirium (Fig. 11).

Another study looked at the effectiveness of proactive geriatric consultation compared with usual care (ie, control group) in reducing delirium in

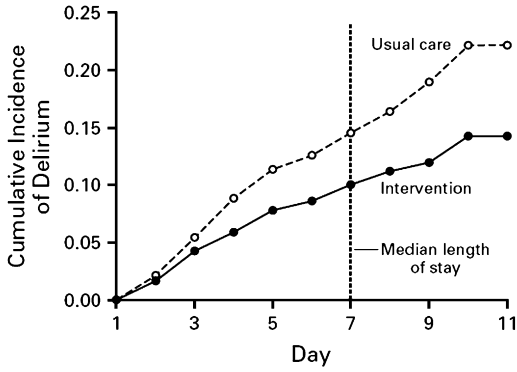

Fig. 11. A multicomponent intervention to prevent delirium in hospitalized older patients. (*From* Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):674; with permission. Copyright © 1999, Massachusetts Medical Society.)

a group of patients 65 and older ($n = 126$) admitted emergently for surgical repair of hip fracture [114]. There were no statistical differences between intervention and control groups regarding baseline measures and characteristics. The results suggest a reduction in the occurrence of delirium in the intervention group (32%) compared with usual care (50%) ($P = .04$), representing a relative risk of 0.64 (95% CI, 0.37–0.98) for the consultation group. One case of delirium was prevented for every 5.6 subjects in the geriatrics consultation group. There was an even greater reduction in cases of "severe delirium," occurring in 12% of intervention subjects and 29% of usual-care subjects, with a relative risk of 0.40 (95% CI, 0.18–0.89). Despite this reduction in delirium, length of stay did not significantly differ between intervention and usual-care groups (median ± interquartile range = 5 ± 2 days in both groups), likely because protocols and pathways predetermined length of stay.

Lundström and colleagues [268] randomly assigned elderly patients ($n = 190$) after femoral neck fracture repair to postoperative care in a specialized geriatric ward (ie, intervention group) or a conventional orthopedic ward. The intervention consisted of staff education focusing on the assessment, prevention, and treatment of delirium and associated complications. As a result of the intervention, the number of days of postoperative delirium was fewer (5.0 ± 7.1 days versus 10.2 ± 13.3 days, $P = .009$) compared with controls. A lower proportion of intervention subjects were delirious postoperatively than controls (54.9% versus 75.3%, $P = .003$). Similarly, subjects in the intervention group suffered from fewer complications (eg, decubitus ulcers, urinary tract infections, nutritional complications, sleeping problems, and falls). Overall, the total postoperative hospitalization was shorter in the intervention ward (28.0 ± 17.9 days versus 38.0 ± 40.6 days, $P = .028$), suggesting that prevention methods can have a significant impact on

postoperative delirium, resulting in fewer days of delirium, lower incidence of medical complications, and shorter length of hospitalization.

Others have studied the use of light therapy as a method of maintaining or restoring the natural circadian rhythm [269]. The investigators followed patients ($n = 11$) after esophageal cancer and after removal of the endotracheal tube. Subjects were either exposed to therapeutic lighting (ie, 5,000 lx at a distance from the light source of 100 cm; study group), or placed in a natural lighting environment (control group) after extubation. The study found that the incidence of delirium was 16% in the study group compared with 40% in the control, group suggesting that alterations in circadian rhythm may serve as a possible contributor to the development of delirium. It also suggests that light therapy may serve as potential prophylaxis or treatment option.

Finally, a Cochrane database review study was conducted (searching the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group and searches in MEDLINE, EMBASE, CINAHL and PsycINFO for delirium prevention trials; searched on October 28, 2005) to assess the effectiveness of interventions for preventing delirium in hospitalized patients [270]. The final analysis included only six randomized, controlled trials. The researchers found there was heterogeneity in methods, participants, and outcomes examined. The investigators concluded that at the time of their search there was little evidence from delirium prevention studies to guide clinical practice. In summary, there was no trial evidence available on the effectiveness of pharmacologic strategies. Based on a single study, the investigators suggest that prophylactic low-dose haloperidol may reduce severity and duration of delirium episodes and shorten length of hospital admission in hip surgery, but that further studies of delirium prevention are needed. A study on the proactive use of geropsychiatric consultations showed favorable results in reducing the severity and duration of postoperative hip surgery.

Summary

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances. It is also the most common psychiatric syndrome found in the general hospital setting, its prevalence surpassing most commonly known psychiatric syndromes. In addition to causing distress to patients, families, and medical caregivers, the development of delirium in general, and postoperative delirium in particular, has been associated with increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, decreased quality of life, prolonged hospital stays, and increased placement in specialized intermediate and long term care facilities. Given increasing evidence that delirium is not always reversible and the many sequelae associated with its development, physicians must do everything possible to prevents its occurrence or shorten its

duration by recognizing its symptoms early, correcting underlying contributing causes, and using treatment strategies proven to help recover functional status.

References

[1] Adamis D, et al. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry 2007;22(7):688–94.
[2] Lindesay J. The concept of delirium. Dement Geriatr Cogn Disord 1999;10(5):310–4.
[3] Lipowski ZJ. Delirium: how its concept has developed. Int Psychogeriatr 1991;3(2):115–20.
[4] Sydenham Society Lexicon of Medicine. Online etymology dictionary 2001 November 2001 [cited]. Available at: http://www.etymonline.com/index.php?search=delirium&searchmode=none. Accessed March 24 2008.
[5] NIMH. The numbers count: mental disorders in America. Stat 2008.. Available at: http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america.shtml. Accessed March 21 2008.
[6] Bucht G, Gustafson Y, Sandberg O. Epidemiology of delirium. Dement Geriatr Cogn Disord 1999;10(5):315–8.
[7] Fann JR. The epidemiology of delirium: a review of studies and methodological issues. Semin Clin Neuropsychiatry 2000;5(2):64–74.
[8] Folstein MF, et al. The epidemiology of delirium in the community: the Eastern Baltimore Mental Health Survey. Int Psychogeriatr 1991;3(2):169–76.
[9] Levkoff S, et al. Epidemiology of delirium: an overview of research issues and findings. Int Psychogeriatr 1991;3(2):149–67.
[10] Schmidt LG, et al. Epidemiology of toxic delirium due to psychotropic drugs in psychiatric hospitals. Compr Psychiatry 1987;28(3):242–9.
[11] Vazquez F, et al. [Epidemiology of delirium in elderly inpatients]. Medicina (B Aires) 2000;60(5 Pt 1):555–60 [in Spanish].
[12] Speed G, Wynaden D, McGowan S, et al. Prevalence rate of delirium at two hospitals in Western Australia. Australian Journal Of Advanced Nursing 2007;25(1):38–43.
[13] Maldonado JR, Dhami N, Wise L. Clinical implications of the recognition and management of delirium in general medical and surgical wards. Psychosomatics 2003;44(2):157–8.
[14] Ritchie J, Steiner W, Abrahamowicz M. Incidence of and risk factors for delirium among psychiatric inpatients. Psychiatr Serv 1996;47(7):727–30.
[15] Gonzalez M, de Pablo J, Fuente E, et al. Instrument for detection of delirium in general hospitals: adaptation of the confusion assessment method. Psychosomatics 2004;45(5):426–31.
[16] McManus J, et al. Delirium post-stroke. Age Ageing 2007;36(6):613–8.
[17] Fernandez F, Levy JK, Mansell PW. Management of delirium in terminally ill AIDS patients. Int J Psychiatry Med 1989;19(2):165–72.
[18] Uldall KK, et al. Association between delirium and death in AIDS patients. AIDS Patient Care STDS 2000;14(2):95–100.
[19] Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990;263(8):1097–101.
[20] Ely EW, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27(12):1892–900.
[21] Lawlor PG, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 2000;160(6):786–94.
[22] McNicoll L, et al. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003;51(5):591–8.

[23] Valdés M, et al. [Multinational European project and multicenter Spanish study of quality improvement of assistance on consultation-liaison psychiatry in general hospital: clinical profile in Spain]. Med Clin (Barc) 2000;115(18):690–4 [in Spanish].
[24] Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. Arch Intern Med 1995;155(5):461–5.
[25] Vaurio LE, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006;102(4):1267–73.
[26] Ebert AD, et al. Early neurobehavioral disorders after cardiac surgery: a comparative analysis of coronary artery bypass graft surgery and valve replacement. J Cardiothorac Vasc Anesth 2001;15(1):15–9.
[27] Nevin M, et al. Prediction of neurological damage after cardiopulmonary bypass surgery. Use of the cerebral function analysing monitor. Anaesthesia 1989;44(9):725–9.
[28] Shaw PJ, et al. Early intellectual dysfunction following coronary bypass surgery. Q J Med 1986;58(225):59–68.
[29] Smith LW, Dimsdale JE. Postcardiotomy delirium: conclusions after 25 years? Am J Psychiatry 1989;146(4):452–8.
[30] McAlpine JN, Hodgson EJ, Abramowitz S, et al. The incidence and risk factors associated with postoperative delirium in geriatric patients undergoing surgery for suspected gynecologic malignancies. Gynecol Oncol 2008;109:296–302.
[31] Benoit AG, et al. Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. J Vasc Surg 2005;42(5):884–90.
[32] Kawaguchi Y, et al. Postoperative delirium in spine surgery. Spine J 2006;6(2):164–9.
[33] Williams-Russo P, et al. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 1992;40(8):759–67.
[34] Gustafson Y, et al. Acute confusional states in elderly patients treated for femoral neck fracture. J Am Geriatr Soc 1988;36(6):525–30.
[35] Marcantonio ER, et al. Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc 2000;48(6):618–24.
[36] Wacker P, et al. Post-operative delirium is associated with poor cognitive outcome and dementia. Dement Geriatr Cogn Disord 2006;21(4):221–7.
[37] Walzer TA, Herrmann M. [Neuropsychological and psychopathologic changes following cardiac surgical procedures]. Fortschr Neurol Psychiatr 1998;66(2):68–83 [in German].
[38] Maldonado JR, et al. Dexmedetomidine: can it reduce the incidence of ICU delirium in postcardiotomy patients? Psychosomatics 2004;45(2):173.
[39] van der Mast RC, Roest FH. Delirium after cardiac surgery: a critical review. J Psychosom Res 1996;41(1):13–30.
[40] Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med 2004; 18(3):184–94.
[41] Pandharipande P, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):21–6.
[42] Kalisvaart KJ, et al. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. J Am Geriatr Soc 2006;54(5):817–22.
[43] Milstein A, et al. Confusion/delirium following cataract surgery: an incidence study of 1-year duration. Int Psychogeriatr 2002;14(3):301–6.
[44] Lowery DP, Wesnes K, Ballard CG. Subtle attentional deficits in the absence of dementia are associated with an increased risk of post-operative delirium. Dement Geriatr Cogn Disord 2007;23(6):390–4.
[45] Wahlund L, Bjorlin GA. Delirium in clinical practice: experiences from a specialized delirium ward. Dement Geriatr Cogn Disord 1999;10(5):389–92.
[46] Bergmann K, Eastham EJ. Psychogeriatric ascertainment and assessment for treatment in an acute medical ward setting. Age Ageing 1974;3(3):174–88.

[47] Fine A, et al. Fas expression in pulmonary alveolar type II cells. Am J Physiol 1997;273 (1 Pt 1):L64–71.
[48] Kinney JM, et al. Tissue fuel and weight loss after injury. J Clin Pathol Suppl (R Coll Pathol) 1970;4:65–72.
[49] McGee W, Veremakis C, Wilson GL. Clinical importance of tissue oxygenation and use to the mixed venous blood gas. Resmedica 1988;4(2):15–24.
[50] Weissman C, et al. Effect of routine intensive care interactions on metabolic rate. Chest 1984;86(6):815–8.
[51] Basarsky TA, Feighan D, MacVicar BA. Glutamate release through volume-activated channels during spreading depression. J Neurosci 1999;19(15):6439–45.
[52] Iijima T, et al. Relationships between glutamate release, blood flow and spreading depression: real-time monitoring using an electroenzymatic dialysis electrode. Neurosci Res 1998; 32(3):201–7.
[53] Moghaddam B, et al. Temporal relationship between neurotransmitter release and ion flux during spreading depression and anoxia. Can J Physiol Pharmacol 1987;65(5):1105–10.
[54] Shimizu-Sasamata M, et al. Attenuated neurotransmitter release and spreading depression-like depolarizations after focal ischemia in mutant mice with disrupted type I nitric oxide synthase gene. J Neurosci 1998;18(22):9564–71.
[55] Somjen GG, et al. Extracellular ions, hypoxic irreversible loss of function and delayed postischemic neuron degeneration studied in vitro. Acta Physiol Scand Suppl 1989; 582:58.
[56] Somjen GG, et al. Spreading depression-like depolarization and selective vulnerability of neurons. A brief review. Stroke 1990;21(11 Suppl):III179–83.
[57] Busto R, et al. Extracellular release of serotonin following fluid-percussion brain injury in rats. J Neurotrauma 1997;14(1):35–42.
[58] Busto R, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989;20(7):904–10.
[59] Globus MY, et al. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. J Neurochem 1995;65(4):1704–11.
[60] Globus MY, et al. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. J Neurochem 1988; 51(5):1455–64.
[61] Globus MY, et al. Intra-ischemic extracellular release of dopamine and glutamate is associated with striatal vulnerability to ischemia. Neurosci Lett 1988;91(1):36–40.
[62] Globus MY, et al. Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. J Cereb Blood Flow Metab 1989;9(6):892–6.
[63] Globus MY, et al. Ischemia induces release of glutamate in regions spared from histopathologic damage in the rat. Stroke 1990;21(11 Suppl):III43–6.
[64] Globus MY, et al. Ischemia-induced extracellular release of serotonin plays a role in CA1 neuronal cell death in rats. Stroke 1992;23(11):1595–601.
[65] Takagi K, et al. Effect of hyperthermia on glutamate release in ischemic penumbra after middle cerebral artery occlusion in rats. Am J Physiol 1994;267(5 Pt 2):H1770–6.
[66] Aakerlund LP, Rosenberg J. Postoperative delirium: treatment with supplementary oxygen. Br J Anaesth 1994;72(3):286–90.
[67] Whitney JF, Gannon DE. Obstructive sleep apnea presenting as acute delirium. Am J Emerg Med 1996;14(3):270–1.
[68] Clayer M, Bruckner J. Occult hypoxia after femoral neck fracture and elective hip surgery. Clin Orthop Relat Res 2000;(370):265–71.
[69] Miyamoto E, Tomimoto H, Nakao Si S, et al. Caudoputamen is damaged by hypocapnia during mechanical ventilation in a rat model of chronic cerebral hypoperfusion. Stroke 2001;32(12):2920–5.
[70] Lipowski ZJ. Delirium (acute confusional states). JAMA 1987;258(13):1789–92.

[71] Berger M, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. Am J Psychiatry 1997;154(6):870–2.
[72] Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Br Med J (Clin Res Ed) 1985;290(6474):1029–32.
[73] Kress JP, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20):1471–7.
[74] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996; 275(11):852–7.
[75] Gaudreau JD, et al. Association between psychoactive medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005;46(4):302–16.
[76] Tune L, et al. Association of anticholinergic activity of prescribed medications with postoperative delirium. J Neuropsychiatry Clin Neurosci 1993;5(2):208–10.
[77] Brauer C, et al. The cause of delirium in patients with hip fracture. Arch Intern Med 2000; 160(12):1856–60.
[78] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43(3):183–94.
[79] Tuma R, DeAngelis LM. Altered mental status in patients with cancer. Arch Neurol 2000; 57(12):1727–31.
[80] Morita T, et al. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 2001;22(6):997–1006.
[81] Olofsson SM, et al. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. Support Care Cancer 1996;4(5):351–7.
[82] Kobayashi K, et al. Severe delirium due to basal forebrain vascular lesion and efficacy of donepezil. Prog Neuropsychopharmacol Biol Psychiatry 2004;28(7):1189–94.
[83] Tune L, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992;149(10):1393–4.
[84] Tune LE. Serum anticholinergic activity levels and delirium in the elderly. Semin Clin Neuropsychiatry 2000;5(2):149–53.
[85] Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001; 62(Suppl 21):11–4.
[86] Tune LE, et al. Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2(8248):651–3.
[87] Flacker JM, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6(1):31–41.
[88] Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987;144(9):1218–20.
[89] Milusheva E, et al. Inhibitory effect of hypoxic condition on acetylcholine release is partly due to the effect of adenosine released from the tissue. Brain Res Bull 1990;24(3): 369–73.
[90] Tune LE, Egeli S. Acetylcholine and delirium. Dement Geriatr Cogn Disord 1999;10(5): 342–4.
[91] Tune L, Folstein MF. Post-operative delirium. Adv Psychosom Med 1986;15:51–68.
[92] Blazer DG 2nd, et al. The risk of anticholinergic toxicity in the elderly: a study of prescribing practices in two populations. J Gerontol 1983;38(1):31–5.
[93] Han L, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161(8):1099–105.
[94] Marcantonio ER, et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272(19):1518–22.

[95] Meuret P, et al. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 2000;93(3):708–17.
[96] Pain L, et al. Central cholinergic depletion induced by 192 IgG-saporin alleviates the sedative effects of propofol in rats. Br J Anaesth 2000;85(6):869–73.
[97] Wang Y, et al. Age-related modifications of effects of ketamine and propofol on rat hippocampal acetylcholine release studied by in vivo brain microdialysis. Acta Anaesthesiol Scand 2000;44(1):112–7.
[98] Olofsson K, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. Acta Anaesthesiol Scand 2004;48(6):679–84.
[99] Kudoh A, et al. Postoperative confusion increases in elderly long-term benzodiazepine users. Anesth Analg 2004;99(6):1674–8 table of contents.
[100] Tune LE, Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. Int Psychogeriatr 1991;3(2):397–408.
[101] Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 2006;102(4):1255–66.
[102] Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother 2007;21(1):15–25.
[103] Wang Y, et al. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry 2007;15(1):50–9.
[104] Gaudreau JD, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. Cancer 2007;109(11):2365–73.
[105] Morrison RS, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003;58(1):76–81.
[106] Morita T, et al. Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial. J Pain Symptom Manage 2005;30(1):96–103.
[107] Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. J Pain Symptom Manage 2004;27(3):268–73.
[108] Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. Med Hypotheses 2005;64(3):471–5.
[109] Litaker D, et al. Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 2001;23(2):84–9.
[110] Bucerius J, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 2004;127(1):57–64.
[111] Eissa A, Andrew MJ, Baker RA. Postoperative confusion assessed with the Short Portable Mental Status Questionnaire. ANZ J Surg 2003;73(9):697–700.
[112] Eriksson M, et al. Delirium after coronary bypass surgery evaluated by the organic brain syndrome protocol. Scand Cardiovasc J 2002;36(4):250–5.
[113] Beloosesky Y, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci 2007;62(4):420–6.
[114] Marcantonio ER, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49(5):516–22.
[115] Palmstierna T. A model for predicting alcohol withdrawal delirium. Psychiatr Serv 2001; 52(6):820–3.
[116] Angus DC, et al. Critical care delivery in the United States: distribution of services and compliance with leapfrog recommendations. Crit Care Med 2006;34(4):1016–24.
[117] Ely EW, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–62.
[118] Pompei P, et al. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42(8):809–15.
[119] Murray AM, et al. Acute delirium and functional decline in the hospitalized elderly patient. J Gerontol 1993;48(5):M181–6.

[120] Levkoff SE, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med 1992;152(2):334–40.
[121] Newman MF, et al. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke 2001;32(12):2874–81.
[122] O'Keeff S, Lavan J. The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 1997;45(2):174–8.
[123] 'Never been the same since.' Delirium in older people might have permanent effects on the brain. Harv Health Lett 2007;32(6):4.
[124] Fann JR, et al. Impact of delirium on cognition, distress, and health-related quality of life after hematopoietic stem-cell transplantation. J Clin Oncol 2007;25(10):1223–31.
[125] Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. Ann Med 2000;32(4):257–63.
[126] Milbrandt EB, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32(4):955–62.
[127] Dew MA, et al. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics 2001;42(4):300–13.
[128] DiMartini A, et al. Posttraumatic stress disorder caused by hallucinations and delusions experienced in delirium. Psychosomatics 2007;48(5):436–9.
[129] Jones C, et al. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med 2001;29(3):573–80.
[130] Stukas AA Jr, et al. PTSD in heart transplant recipients and their primary family caregivers. Psychosomatics 1999;40(3):212–21.
[131] Leslie DL, et al. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168(1):27–32.
[132] Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med 1994; 97(3):278–88.
[133] Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. Arch Intern Med 1995;155(22):2459–64.
[134] Kishi Y, et al. Delirium: patient characteristics that predict a missed diagnosis at psychiatric consultation. Gen Hosp Psychiatry 2007;29(5):442–5.
[135] Rolfson DB, et al. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. Can J Cardiol 1999;15(7): 771–6.
[136] Inouye SK, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113(12):941–8.
[137] Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. Arch Gen Psychiatry 1983;40(7):812.
[138] Dal Pan G, Stern Y, Sano M, et al. Clock-drawing in neurological disorders. Behav Neurol 1989;2:39–48.
[139] Sunderland T, et al. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. J Am Geriatr Soc 1989;37(8):725–9.
[140] APA, Diagnostic and statistical manual of mental disorders. 3rd edition Revised. 1987, Washington, DC: American Psychiatric Association.
[141] Pisani MA, et al. Underrecognition of preexisting cognitive impairment by physicians in older ICU patients. Chest 2003;124(6):2267–74.
[142] APA. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994.
[143] Marcantonio ER, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271(2):134–9.
[144] Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;23(1):89–97.

[145] Ely EW, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29(7): 1370–9.
[146] Trzepacz PT, et al. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001;13(2):229–42.
[147] Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161: 843–5.
[148] Tremont-Lukats IW, Teixeira GM, Hernandez DE. Primitive reflexes in a case-control study of patients with advanced human immunodeficiency virus type 1. J Neurol 1999; 246(7):540–3.
[149] Paulson GW. The neurological examination in dementia. Contemp Neurol Ser. 1977;15: 169–88.
[150] Liu CY, Hsieh JC. [Post cardiopulmonary-bypass neuropsychiatric complications]. Changgeng Yi Xue Za Zhi 1993;16(1):52–8 [in Chinese].
[151] Engel GL, Webb JP, Ferris EB. Quantitative electroencephalographic studies of anoxia in humans: comparison with acute alcoholic intoxication and hypoglycemia. J Clin Invest 1945;24(5):691–7.
[152] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. J Chronic Dis 1959; 9(3):260–77.
[153] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. 1959. J Neuropsychiatry Clin Neurosci 2004;16(4):526–38.
[154] Koponen H, et al. Computed tomography findings in delirium. J Nerv Ment Dis 1989; 177(4):226–31.
[155] Koponen H, et al. EEG spectral analysis in delirium. J Neurol Neurosurg Psychiatry 1989; 52(8):980–5.
[156] Koponen H, et al. Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one-year follow-up. Acta Psychiatr Scand 1989;79(6): 579–85.
[157] Plaschke K, et al. EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. Anaesthesia 2007;62(12):1217–23.
[158] Romano J, Engel G. Delirium. I. EEG data. Arch Neurol Psychiatry 1944;51:356–77.
[159] Trzepacz PT, Leavitt M, Ciongoli K. An animal model for delirium. Psychosomatics 1992; 33(4):404–15.
[160] Trzepacz PT, Sclabassi RJ, van Thiel DH. Delirium: a subcortical phenomenon? J Neuropsychiatry Clin Neurosci 1989;1(3):283–90.
[161] Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. Semin Clin Neuropsychiatry 2000;5(2):75–85.
[162] Meagher DJ, et al. Relationship between symptoms and motoric subtype of delirium. J Neuropsychiatry Clin Neurosci 2000;12(1):51–6.
[163] Inouye SK, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119(6):474–81.
[164] Adams F, Fernandez F, Andersson BS. Emergency pharmacotherapy of delirium in the critically ill cancer patient. Psychosomatics 1986;27(1 Suppl):33–8.
[165] Fernandez F, et al. Treatment of severe, refractory agitation with a haloperidol drip. J Clin Psychiatry 1988;49(6):239–41.
[166] Inouye SK, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340(9):669–76.
[167] Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med 1994;22(3):433–40.
[168] Sanders KM, Minnema MA, Murray GB. Low incidence of extrapyramidal symptoms in treatment of delirium with intravenous haloperidol and lorazepam in the intensive care unit. J Intensive Care Med 1989;4(5):201–4.

[169] Ziehm SR. Intravenous haloperidol for tranquilization in critical care patients: a review and critique. AACN Clin Issues Crit Care Nurs 1991;2(4):765–77.
[170] Adams F. Neuropsychiatric evaluation and treatment of delirium in cancer patients. Adv Psychosom Med 1988;18:26–36.
[171] Ayd FJ Jr. Haloperidol: twenty years' clinical experience. J Clin Psychiatry 1978;39(11):807–14.
[172] Sanders KM, Murray GB, Cassem NH. High-dose intravenous haloperidol for agitated delirium in a cardiac patient on intra-aortic balloon pump. J Clin Psychopharmacol 1991;11(2):146–7.
[173] Segatore M, Adams D. Managing delirium and agitation in elderly hospitalized orthopaedic patients: Part 2—interventions. Orthop Nurs 2001;20(2):61–73 [quiz: 73–5].
[174] Stern TA. Continuous infusion of haloperidol in agitated, critically ill patients. Crit Care Med 1994;22(3):378–9.
[175] Tesar GE, Murray GB, Cassem NH. Use of high-dose intravenous haloperidol in the treatment of agitated cardiac patients. J Clin Psychopharmacol 1985;5(6):344–7.
[176] Maldonado J, Kang H. Evidence of decreased incidence of extra-pyramidal symptoms with intravenous haloperidol. J Psychosom Res 2003;55:140–1.
[177] Maldonado JR, Dhami N. Recognition and management of delirium in the medical and surgical intensive care wards. J Psychosom Res 2003;55(2):150.
[178] APA. Diagnostic and statistical manual of mental disorders. 3rd edition. Washington, DC: American Psychiatrc Association; 1980.
[179] Tune L. The role of antipsychotics in treating delirium. Curr Psychiatry Rep 2002;4(3):209–12.
[180] Wilt JL, et al. Torsade de Pointes associated with the use of intravenous haloperidol. Ann Intern Med 1993;119(5):391–4.
[181] Darpo B. Spectrum of drugs prolonging QT interval and the incidence of Torsade de Pointes. Eur Heart J Suppl 2001;3(suppl K):K70–80.
[182] Justo D, et al. Torsade de Pointes induced by psychotropic drugs and the prevalence of its risk factors. Acta Psychiatr Scand 2005;111(3):171–6.
[183] Yap YG, Camm AJ. Drug induced QT prolongation and Torsades de Pointes. Heart 2003; 89(11):1363–72.
[184] Lawrence KR, Nasraway SA. Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. Pharmacotherapy 1997;17(3):531–7.
[185] Shapiro BA, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. Crit Care Med 1995;23(9):1596–600.
[186] Jacobi J, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30(1):119–41.
[187] Khasati N, Thompson J, Dunning J. Is haloperidol or a benzodiazepine the safest treatment for acute psychosis in the critically ill patient? Interact Cardiovasc Thorac Surg 2004;3(2): 233–6.
[188] FDA. Information for healthcare professionals: Haloperidol (marketed as Haldol, Haldol decanoate and Haldol lactate) 2007. [cited]; Available at: www.fda.gov/cder/drug/InfoSheets/HCP/haloperidol.htm. Accessed March 26 2008.
[189] Bender S, et al. Severe adverse drug reactions in psychiatric inpatients treated with neuroleptics. Pharmacopsychiatry 2004;37(Suppl 1):S46–53.
[190] Leucht S, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003;361(9369):1581–9.
[191] Henderson DC. Managing weight gain and metabolic issues in patients treated with atypical antipsychotics. J Clin Psychiatry 2008;69(2):e04.
[192] Horikawa N, et al. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. Gen Hosp Psychiatry 2003;25(4):289–92.
[193] Mittal D, et al. Risperidone in the treatment of delirium: results from a prospective open-label trial. J Clin Psychiatry 2004;65(5):662–7.

[194] Parellada E, et al. Risperidone in the treatment of patients with delirium. J Clin Psychiatry 2004;65(3):348–53.
[195] Chen B, Cardasis W. Delirium induced by lithium and risperidone combination. Am J Psychiatry 1996;153(9):1233–4.
[196] Morikawa M, Kishimoto T. Probable dementia with lewy bodies and risperidone-induced delirium. Can J Psychiatry 2002;47(10):976.
[197] Tavcar R, Dernovsek MZ. Risperidone-induced delirium. Can J Psychiatry 1998;43(2): 194.
[198] Kato D, et al. Delirium resolving upon switching from risperidone to quetiapine: implication of CYP2D6 genotype. Psychosomatics 2005;46(4):374–5.
[199] Torres R, Mittal D, Kennedy R. Use of quetiapine in delirium: case reports. Psychosomatics 2001;42(4):347–9.
[200] Al-Samarrai S, et al. Quetiapine for treatment-resistant delirium. Psychosomatics 2003; 44(4):350–1.
[201] Sasaki Y, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. J Clin Psychiatry 2003;64(11):1316–21.
[202] Kim KY, et al. Treatment of delirium in older adults with quetiapine. J Geriatr Psychiatry Neurol 2003;16(1):29–31.
[203] Pae CU, et al. A pilot trial of quetiapine for the treatment of patients with delirium. Hum Psychopharmacol 2004;19(2):125–7.
[204] Maneeton B, Maneeton N, Srisurapanont M. An open-label study of quetiapine for delirium. J Med Assoc Thai 2007;90(10):2158–63.
[205] Balit CR, et al. Quetiapine poisoning: a case series. Ann Emerg Med 2003;42(6):751–8.
[206] Sim FH, Brunet DG, Conacher GN. Quetiapine associated with acute mental status changes. Can J Psychiatry 2000;45(3):299.
[207] Kim KS, et al. An open pilot trial of olanzapine for delirium in the Korean population-Psychiatry Clin Neurosci 2001;55(5):515–9.
[208] Passik SD, Cooper M. Complicated delirium in a cancer patient successfully treated with olanzapine. J Pain Symptom Manage 1999;17(3):219–23.
[209] Halil M, Cankurtaran ES, Ozkayar N, et al. Elderly patient with delirium after myocardial infarction. J Natl Med Assoc 2006;98(4):648–50.
[210] Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002;43(3):175–82.
[211] Breitbart W, et al. The memorial delirium assessment scale. J Pain Symptom Manage 1997; 13(3):128–37.
[212] Robinson RL, Burk MS, Raman S. Fever, delirium, autonomic instability, and monocytosis associated with olanzapine. J Postgrad Med 2003;49(1):96.
[213] Steil B. [A case of delirium after olanzapine intoxication]. Nervenarzt 2003;74(11):1009–11 [in German].
[214] Morita T, et al. Olanzapine-induced delirium in a terminally ill cancer patient. J Pain Symptom Manage 2004;28(2):102–3.
[215] Samuels S, Fang M. Olanzapine may cause delirium in geriatric patients. J Clin Psychiatry 2004;65(4):582–3.
[216] Prommer E. Re: olanzapine-induced delirium. J Pain Symptom Manage 2005;29(2):119–20.
[217] Arora M, Praharaj SK. Nonfatal suicidal olanzapine overdose: a case report. Clin Neuropharmacol 2006;29(4):190–1.
[218] Lim CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? Ann Pharmacother 2006;40(1):135–8.
[219] Morgan M, Hackett LP, Isbister GK. Olanzapine overdose: a series of analytically confirmed cases. Int Clin Psychopharmacol 2007;22(3):183–6.
[220] Alao AO, Moskowitz L. Aripiprazole and delirium. Ann Clin Psychiatry 2006;18(4):267–9.
[221] Straker DA, Shapiro PA, Muskin PR. Aripiprazole in the treatment of delirium. Psychosomatics 2006;47(5):385–91.

[222] Leso L, Schwartz TL. Ziprasidone treatment of delirium. Psychosomatics 2002;43(1): 61–2.
[223] Young CC, Lujan E. Intravenous ziprasidone for treatment of delirium in the intensive care unit. Anesthesiology 2004;101(3):794–5.
[224] Takeuchi T, et al. Perospirone in the treatment of patients with delirium. Psychiatry Clin Neurosci 2007;61(1):67–70.
[225] Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. Psychosomatics 1998;39(5):422–30.
[226] Schwartz TL, Masand PS. Treatment of delirium with quetiapine. Prim Care Companion J Clin Psychiatry 2000;2(1):10–2.
[227] Skrobik YK, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting-Intensive Care Med 2004;30(3):444–9.
[228] Liu CY, et al. Efficacy of risperidone in treating the hyperactive symptoms of delirium. Int Clin Psychopharmacol 2004;19(3):165–8.
[229] Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004;45(4):297–301.
[230] Lonergan E, et al. Antipsychotics for delirium. Cochrane Database Syst Rev 2007;(2): CD005594.
[231] Ozbolt LB, Paniagua MA, Kaiser RM. Atypical antipsychotics for the treatment of delirious elders. J Am Med Dir Assoc 2008;9(1):18–28.
[232] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294(15):1934–43.
[233] Raivio MM, et al. Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. Am J Geriatr Psychiatry 2007;15(5):416–24.
[234] Lindborg SR, et al. Effects of intramuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients. Psychiatry Res 2003;119(1–2):113–23.
[235] Vieweg WV. New generation antipsychotic drugs and QTc interval prolongation. Prim Care Companion J Clin Psychiatry 2003;5(5):205–15.
[236] Dautzenberg PL, et al. Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage. Int J Geriatr Psychiatry 2004;19(7):641–4.
[237] van den Bliek BM, Maas HA. [Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine]). Ned Tijdschr Geneeskd 2004;148(43):2149, author reply 2149 [in Dutch].
[238] Bayindir O, et al. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. J Thorac Cardiovasc Surg 2001;121(1):176–7.
[239] Farina ML, Levati A, Tognoni G. A multicenter study of ICU drug utilization. Intensive Care Med 1981;7(3):125–31.
[240] Maldonado JR, van der Starre PJ, Block T, et al. Post-operative sedation and the incidence of delirium and cognitive deficits in cardiac surgery patients. Anesthesiology 2003;99:465.
[241] Maldonado J, Wysong A, van der Starre PJA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics 2008, in press.
[242] Diegeler A, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 2000;69(4):1162–6.
[243] Tucker LA. Post-pump delirium. Intensive Crit Care Nurs 1993;9(4):269–73.
[244] Van Dijk D, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 2002;287(11):1405–12.
[245] Brown T. Basic mechanisms in the pathogenesis of delirium. In: Stoudemire AFB, Greenberg DB, editors. The psychiatric care of the medical patient. New York: Oxford Press; 2000. p. 571–80.
[246] Ross CA. CNS arousal systems: possible role in delirium. Int Psychogeriatr 1991;3(2):353–71.

[247] Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000;5(2):132–48.
[248] Nakamura J, et al. Does plasma free-3-methoxy-4-hydroxyphenyl(ethylene)glycol increase in the delirious state? A comparison of the effects of mianserin and haloperidol on delirium. Int Clin Psychopharmacol 1997;12(3):147–52.
[249] Hsu YW, et al. Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004;101(5):1066–76.
[250] Seaman JS, et al. Impaired oxidative metabolism precipitates delirium: a study of 101 ICU patients. Psychosomatics 2006;47(1):56–61.
[251] Buttermann AE, Reid K, Maze M. Are cholinergic pathways involved in the anesthetic response to alpha2 agonists. Toxicol Lett 1998;100–101:17–22.
[252] Aho M, et al. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology 1991;74(6):997–1002.
[253] Weinbroum AA, Ben-Abraham R. Dextromethorphan and dexmedetomidine: new agents for the control of perioperative pain. Eur J Surg 2001;167(8):563–9.
[254] Crawford RD, Baskoff JD. Fentanyl-associated delirium in man. Anesthesiology 1980; 53(2):168–9.
[255] Maddocks I, et al. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. J Pain Symptom Manage 1996;12(3):182–9.
[256] Nelson LE, et al. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003; 98(2):428–36.
[257] Scholz J, Tonner PH. α2-adrenoreceptor agonists in anaesthesia: a new paradigm. Curr Opin Anaesthesiol 2000;13:437–42.
[258] Maier C, et al. Neuroprotection by the alpha 2-adrenoreceptor agonist dexmedetomidine in a focal model of cerebral ischemia. Anesthesiology 1993;79(2):306–12.
[259] Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med 2003;114(9):742–52.
[260] Schrader SL, et al. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. Neurologist 2008;14(2):134–7.
[261] Kalisvaart KJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53(10): 1658–66.
[262] Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007;35(5):714–9.
[263] Larsen KA, Kelly S, Stern TA, et al. Randomized, placebo-controlled study of perioperative administration of olanzapine to prevent post-operative delirium in joint replacement patients; In Academy of Psychosomatic Medicine. 2007: Amalia Island (FL).
[264] Liptzin B, et al. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry 2005;13(12):1100–6.
[265] Sampson EL, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry 2007;22(4):343–9.
[266] Moretti R, et al. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. Am J Alzheimers Dis Other Demen 2004;19(6):333–9.
[267] Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. Paediatr Anaesth 2007;17(9):846–50.
[268] Lundström M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. Aging Clin Exp Res 2007;19(3):178–86.

[269] Taguchi T, Yano M, Kido Y. Influence of bright light therapy on postoperative patients: a pilot study. Intensive Crit Care Nurs 2007;23(5):289–97.
[270] Siddiqi N, et al. Interventions for preventing delirium in hospitalised patients. Cochrane Database Syst Rev 2007;(2): CD005563.
[271] Hart RP, Levenson JL, Sessler CN, et al. Validation of a cognitive test for delirium in medical ICU patients. Psychosomatics 1996;37(6):533–46.
[272] Robertsson B, Karlsson I, Styrud E, et al. Confusional State Evaluation (CSE): an instrument for measuring severity of delirium in the elderly. Br J Psychiatry 1997;170: 565–70.
[273] O'keeffe S. Rating the severity of delirium: the delirium assessment scale. International Journal of Geriatric Psychiatry 1994;9(7):551–6.
[274] Otter H, Martin J, Basell K, et al. Validity and reliability of the DDS for severity of delirium in the ICU. Neurocritical Care 2005;2(2):150–8.
[275] McCusker J, Cole M, Bellavance F, et al. Reliability and validity of a new measure of severity of delirium. International Psychogeriatrics/IPA 1998;10(4):421–33.
[276] Bettin KM, Maletta GJ, Dysken MW, et al. Measuring delirium severity in older general hospital inpatients without dementia. The Delirium Severity Scale. Am J Geriatr Psychiatry 1998;6(4):296–307.
[277] Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. Journal of Geriatric Psychiatry and Neurology 1992;5(1):14–21.
[278] Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. Journal of the American Geriatrics Society 1975; 23(10):433–41.
[279] Bland RC, Newman SC. Mild dementia or cognitive impairment: the Modified Mini-Mental State examination (3MS) as a screen for dementia. Canadian Journal of Psychiatry 2001;46(10):506–10.
[280] O'Donnell WE, Reynolds DM, De Soto CB. Neuropsychological impairment scale (NIS): initial validation study using trailmaking test (A & B) and WAIS digit symbol (scaled score) in a mixed grouping of psychiatric, neurological, and normal patients. J Clin Psychol 1983; 39(5):746–8.
[281] Burt T. Donepezil and related cholinesterase inhibitors as mood and behavioral controlling agents. Current Psychiatry Reports 2000;2(6):473–8.
[282] Bruera E, Strasser F, Shen L, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. Journal of Pain and Symptom Management 2003;26(5):1049–54.
[283] Fisher RS, Bortz JJ, Blum DE, et al. A Pilot Study of Donepezil for Memory Problems in Epilepsy. Epilepsy Behav 2001;2(4):330–4.
[284] Gleason OC. Donepezil for postoperative delirium. Psychosomatics 2003;44(5):437–8.
[285] Haase U, Rundshagen I. Pharmacotherapy–physostigmine administered post-operatively. Anasthesiol Intensivmed Notfallmed Schmerzther 2007;42(3):188–9.
[286] Hori K, Tominaga I, Inada T, et al. Donepezil-responsive alcohol-related prolonged delirium. Psychiatry and Clinical Neurosciences 2003;57(6):603–4.
[287] Kaufer DI, Catt KE, Lopez OL, et al. Dementia with Lewy bodies: response of delirium-like features to donepezil. Neurology 1998;51(5):1512.
[288] Logan CJ, Stewart JT. Treatment of post-electroconvulsive therapy delirium and agitation with donepezil. The Journal of ECT 2007;23(1):28–9.
[289] Palmer TR. Donepezil in advanced dementia, or delirium? Journal of the American Medical Directors Association 2004;5(1):67.
[290] Rabinowitz T. Delirium: an important (but often unrecognized) clinical syndrome. Current Psychiatry Reports 2002;4(3):202–8.
[291] Weizberg M, Su M, Mazzola JL, et al. Altered mental status from olanzapine overdose treated with physostigmine. Clinical Toxicology 2006;44(3):319–25.

[292] Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. Journal of Geriatric Psychiatry and Neurology 1998;11(3):159–61.
[293] Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. Journal of the American Geriatrics Society 1999;47(3):379–80.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 723–736

CRITICAL
CARE
CLINICS

Detection and Management of Pre-existing Cognitive Impairment and Associated Behavioral Symptoms in the Intensive Care Unit

Hochang B. Lee, MD[a,*], Candyce J. DeLoatch, MD[a], SeongJin Cho, MD, PhD[a], Paul Rosenberg, MD[a], Simon C. Mears, MD, PhD[b], Frederick E. Sieber, MD[c]

[a]*Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287–5371, USA*
[b]*Department of Orthopedic Surgery, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287–5371, USA*
[c]*Department of Anesthesiology, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287–5371, USA*

The elderly (65+) population, comprised of 36.3 million people, is the fastest growing sector of the United States population [1]. Most of the 5 million elders suffering from dementia in the United States belong to this age group, and the number of dementia cases in the United States is expected to triple unless a cure or a preventive strategy is developed [2]. This rapid increase in the elderly population and the associated incidence of dementia cases is of critical importance to ICUs around the country because patients in this age group currently account for 42% to 52% of ICU admissions [3,4] and for more than half of all ICU days [5].

With or without pre-existing cognitive impairments, such as mild cognitive impairment (MCI) or dementia, the application of critical care provides life-saving benefit to older persons. Pre-existing cognitive impairment does put a patient at heightened risk for complications from intensive care interventions because of their increased vulnerability. For example, patients with dementia have been known to be at the highest risk for developing delirium and subsequent poor ICU outcomes [6]. Although the detection and management of delirium has garnered much interest from critical care specialists,

* Corresponding author.
E-mail address: Hochang@jhmi.edu (H.B. Lee).

doi:10.1016/j.ccc.2008.05.006

sparse data are available to guide intensivists in detection and care of patients with dementia in the ICU. This article reviews broadly the available literature on the impact of pre-existing cognitive impairment in care of ICU patients and provides an overview on detection and care of dementia patients for clinicians in the ICU setting.

Definitions of delirium and pre-existing cognitive impairment

Delirium is a disorder of sensorium or level of consciousness. Consciousness, defined as a function of the nervous system, is concerned with the perceptual experience of information from the environment and from one's own body. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) defines delirium as a syndrome of disturbed consciousness, which results in a change in cognition (memory, disorientation, or language disturbance) or in perception from baseline, and is not caused by dementia [7].

Dementia is defined as "global decline of cognitive capacity in clear consciousness" [8]. There are three elements to the definition of dementia. First, the term "global" means that multiple areas of cognition are impaired. Unlike aphasia or amnestic syndrome, dementia means that more than one area of cognition is impaired. In addition to impairment in memory, other cognitive domains, such as language, abstraction, calculation, perception, and judgment, are impaired. Second, "decline" means deterioration from previous level of cognitive capacity. This element distinguishes dementia from other cognitive disorders, such as mental retardation and learning disorders, which are present from birth. Additionally, the level of decline should be severe enough to impair one's daily activities. This level of decline distinguishes dementia from MCI. Finally, "in clear consciousness" means that the level of consciousness is not impaired. This element distinguishes dementia from delirium. Box 1 lists the DSM-IV criteria for the diagnosis of dementia of the Alzheimer's type, the most common form of dementia [7].

Most patients with dementia experience measurable cognitive decline before actually meeting the criteria for dementia [9]. The clinical entity of MCI represents the boundary of normal aging and early dementia. It refers generally to complaints of memory functioning in elderly people, which are judged to have a high probability of progressing toward Alzheimer's dementia. The cognitive deficits in a MCI patient are detectable, yet unlike in a patient with dementia, they are not severe enough to impair daily activities (Box 2) [9]. It has been estimated that 17% of the elderly population meet criteria for MCI [10,11], and of those, 10% to 15% progress to dementia every year compared with healthy control subjects [12,13]. "Pre-existing cognitive impairment" (PCI) is a broader term that refers to either dementia or MCI that is present in chronic form before hospital admission [14]. This

Box 1. DSM-IV criteria for the diagnosis of dementia of the Alzheimer's type

A. The development of multiple cognitive deficits manifested by both
   1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
   2. One or more of the following cognitive disturbances
      (a) Aphasia (language disturbance)
      (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) Agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) Disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
C. The course is characterized by gradual onset and continuing cognitive decline
D. The cognitive deficits in criteria A1 and A2 are not caused by any of the following
   (1) Other central nervous system conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) Systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) Substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium

distinguishes pre-existing cognitive impairment from delirium or cognitive impairments that may result directly from the illness or hospitalization.

Pre-existing cognitive impairment and incidence of delirium in the ICU

Based on a sample of medical ICU patients above age 65, Pisani and colleagues reported prevalence estimates of pre-existing cognitive impairment to be approximately 31% to 37% [14,15]. These figures double the

Box 2. Criteria for amnestic MCI

Memory complaint, preferably corroborated by an informant
Impaired memory function for age and education
Preserved general cognitive function
Intact activities of daily living
Absence of dementia

Data from Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–42.

prevalence rates of cognitive impairment reported for community dwelling (10%–18%) and hospitalized non-ICU (20%) patients with pre-existing cognitive impairment [14]. The same study found that patients who have pre-existing cognitive impairments are significantly older, more likely to be women, less likely to be currently married, more likely to have been admitted to the ICU from a nursing home, and more likely to have higher APACHE II scores on ICU admission [14]. Between patients with and without pre-existing cognitive impairments, however, no difference was found between the two groups in terms of characteristics, such as education, number of comorbidities on admission, code status on admission, and admission from respiratory or cardiac causes [14].

Delirium is very common in the ICU with a reported prevalence of nearly 70% to 87% among patients [16–18]. Delirium causes increased morbidity, mortality, nursing home placement, longer ICU and hospital stays, and costlier hospitalizations [19–21]. In patients who receive mechanical ventilator assistance, delirium is a predictor of 6-month mortality [22]. Patients with one episode of delirium had a 40% increase in length of stay in the ICU and total hospital costs, after controlling for confounding variables, compared with patients with no delirium [20].

Several previous studies have demonstrated that dementia is an important risk factor for delirium [23–26]. A recent cohort study of 304 medical ICU patients 60 years of age or older reported that dementia was the strongest risk factor for delirium (odds ratio [OR], 6.3; 95% confidence interval [CI], 2.9–13.8) [18]. Other risk factors included the administration of benzodiazepines before ICU admission (OR, 3.4; 95% CI, 1.6–7); an elevated creatinine level (OR, 2.1; 95% CI, 1.1–4); and low arterial pH (OR, 2.1; 95% CI, 1.1–3.9). Delirium is listed as one of the six leading causes of preventable injury in those older than 65 years [27]. For patients with pre-existing cognitive impairments, an ICU clinician should be even more vigilant about detection and treatment of delirium to reduce the associated high morbidity and mortality [22].

Detection of pre-existing cognitive impairment in the ICU

Cognitive impairment in medical units is often unrecognized and untreated by hospital physicians [28,29]. In a study of 163 medical inpatients in which the prevalence of cognitive impairment was 31%, attending physicians recognized the cognitive impairment in only 13% of cases and junior medical staff recognized it in only 9% of cases [28]. Most patients admitted to an acute care hospital do not have prior documentation of their cognitive function [30,31]. Because ICU physicians primarily rely on past medical records from referring physicians to obtain information about a patient's baseline cognitive status, pre-existing cognitive impairment may not be appropriately evaluated or managed. In a cohort of 163 acute medical ward patients aged 65 and older, attending physicians were unaware of the existence of previous cognitive impairment in 53% of cases, and intern physicians were unaware in 59% of cases [32].

The biggest barrier to detection of pre-existing cognitive impairment is the fact that direct, in-depth assessment of cognitive functioning is impractical in the ICU setting because of multiple factors, such as mechanical ventilation, related communication difficulties, sedation, wounds, and patient fatigue. Delirium can be diagnosed reliably and rapidly with the Intensive Care Delirium Screening Checklist [33] or the Confusion Assessment Method for the Intensive Care Unit [16]. Additionally, the Mini-Mental State Examination [34] is a popular, brief cognitive screening tool that can detect severity of global cognitive impairment. None of the aforementioned instruments, however, provides any information about a patient's cognitive state before the acute illness. Without information on the previous level of function or cognition, a low score on Mini-Mental State Examination could be a reflection of dementia, delirium, or delirium superimposed on dementia. The Mini-Mental State Examination by itself does not help differentiate among these three syndromes.

The use of proxy interview-based assessment of pre-existing cognitive impairment has been examined to aid physicians in the ICU. The Modified Blessed Dementia Rating Scale (MBDRS) [35] and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [36] were specifically developed for proxy administration and have been widely used for identification of pre-existing cognitive impairment in both outpatient and hospital settings. Administration of either instrument takes less than 5 minutes. The MBDRS is an 11-item instrument that has been shown to correlate with pathologic assessment of dementia, to discriminate between demented and nondemented subjects, and to correlate well with objective patient measures of dementia. The IQCODE is a 16-item questionnaire designed to measure cognitive decline over time, providing a longitudinal perspective of cognitive functioning. The IQCODE has also been shown to correlate with direct patient assessment using cognitive screening tests and has been used to evaluate the presence of dementia in non–critically

ill medical inpatients and to predict the development of dementia after hospital discharge.

A recent study found that both IQCODE and MBDRS could be reliably used to detect pre-existing cognitive impairment in the ICU [37]. The choice of instrument to assess pre-existing cognitive impairment depends on the goals of the study. The IQCODE does require a proxy respondent who has observed the patient over a 5-year period. If such proxy is available, IQCODE is more sensitive to detect mild existing cognitive impairment than the MBDRS. In cases in which detection of moderate to severe cognitive impairment is sufficient and in which proxies with knowledge of the 5-year history of the patients may not be consistently available, the MBDRS is recommended.

Management of behavioral and psychologic symptoms of dementia in the ICU

Although the most common cause of agitation, psychosis, and mood symptoms in the intensive care setting is delirium, ICU clinicians should be aware of the common behavioral and psychologic symptoms of dementia (BPSD). BPSD have become increasingly recognized as part and parcel of the progression of MCI and dementia. Such symptoms include affective disorders (eg, depression, anxiety, euphoria); personality change; psychotic symptoms (eg, hallucinations, delusions); and behavioral disturbances (eg, agitation, aggression, aberrant motor behavior or wandering, apathy, irritability, sleep and eating disturbance, disinhibition).

ICU clinicians are likely to encounter BPSD among patients with preexiting cognitive impairment. In the Cardiovascular Healthy Study, among the dementia participants, 75% (N = 270) had exhibited a neuropsychiatric symptom in the past month (62% were clinically significant); 55% (N = 199) reported two or more; and 44% (N = 159) three or more disturbances in the past month [38]. When combined with another study, the 18-month prevalence rate of neuropsychiatric symptoms was estimated to be 88.6% [39]. Symptoms seem to be quite persistent because 81% of those who initially had symptoms continued to have symptoms 18 months later [40].

Prevalence of noncognitive behavioral symptoms in MCI seems to be also much higher than in the general population, but lower than in dementia [38,41]. Based on the Memory and Medical Care Study, Chan and colleagues [41] reported that compared with dementia subjects, those classified as MCI had a lower prevalence (47.1% versus 66.1%) of any symptoms (psychosis, depression, or agitation) and of agitation (24.8% versus 45.1%). In the Cardiovascular Health Study, of the 682 individuals with dementia or MCI, 43% of MCI participants exhibited neuropsychiatric symptoms (29% rated as clinically significant) with depression (20%), apathy (15%), and irritability (15%) being most common, whereas 75% of dementia participants exhibited neuropsychiatric symptoms in the previous month [38].

It is important to distinguish behavioral symptoms of delirium from BPSD. Sometimes, depression can closely mimic mild delirium and MCI, and should be in differential diagnosis of all cognitive evaluations. Table 1 compares the features of delirium, dementia, and depression. Behavioral symptoms of delirium are generally associated with acute impairment in the level of consciousness, along with fluctuating level of symptom severity. BPSD tends to be more stable in severity and does not involve impairment in attention. Often, behavioral symptoms of delirium can be superimposed on pre-existing cognitive impairment. In this case, treatment of underlying cause of delirium should triumph over addressing the behavioral symptoms. The following sections discuss management strategies for specific neuropsychiatric symptoms in the absence of delirium.

Depression

Estimates for the prevalence of major depression in patients with dementia are 20% to 25% [42]. Depressive disorders in dementia are often somewhat different from those occurring in the absence of dementia. Overly relying on DSM-IV diagnostic criteria may result in an underdiagnosis and undertreatment of depression among dementia patients in ICU. For example, patients with depression and dementia may not endorse hopelessness, suicidal thoughts, or worthlessness. Instead, dementia patients express such symptoms as anxiety, anhedonia, irritability, lack of motivation, and agitation [43]. Anxiety is often the most noticeable symptom, and delusions, typically of a paranoid nature, also accompany depression among dementia patients.

Table 1
Comparative features of delirium, dementia, and depression

	Delirium	Dementia	Depression
Definition	Impaired sensorium (reduced level of consciousness)	Global decline in cognitive capacity in clear consciousness	Disturbance in mood, with associated low vital sense and low self-attitude
Core symptoms	Inattention, distractibility, drowsiness, befuddlement	Amnesia, aphasia, agnosia, apraxia, disturbed executive function	Sadness, anhedonia, crying
Common associated symptoms	Cognitive impairment, hallucinations, mood lability	Depression, delusions, hallucinations, irritability	Fatigue, insomnia, anorexia, guilt, self-blame, hopelessness, helplessness
Temporal features	Acute or subacute onset	Chronic onset, usually gradual	Episodic, subacute onset
Diurnal features	Usually worse in the evening and night	No clear pattern	Usually worse in the morning

Nonpharmacologic or behavioral interventions for the treatment of depression are not practical in the ICU setting. Also, given the presence of cognitive impairment, psychotherapy is generally not beneficial. Serotonin-specific reuptake inhibitors have been shown to be efficacious in treatment of depression in Alzheimer's disease [42]. It is important to begin at a low dose of serotonin-specific reuptake inhibitor (eg, about one fourth of the full adult antidepressant dose, such as sertraline 25 mg once a day) and increase slowly as tolerated, closely monitoring for the development of side effects and improvement in mood. It is also important not to undertreat, recognizing that most patients with Alzheimer's disease have optimal responses in the moderate to high dose range (eg, 100 mg of sertraline) of serotonin-specific reuptake inhibitors. Other non–serotonin-specific reuptake inhibitor options for the treatment of depressive symptoms include starting mirtazapine at 7.5 mg before bedtime; bupropion at 100 mg once a day of the extended-release preparation; or serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine starting at 37.5 mg once a day of the extended-release preparation). Table 2 lists common antidepressants and their recommended dosage for treatment of depressive symptoms in patients with MCI or dementia.

Delusions and hallucinations

Although delirium is the most common cause of psychotic symptoms in the ICU, delusions and hallucinations often occur in dementia in the absence of delirium. In the absence of clouded sensorium, attentional disturbance, and sleep-wake cycle disruption, psychosis caused by dementia should be considered and treated accordingly. Delusions associated with dementia tend to occur more commonly than hallucinations. In population-based studies, the prevalence of delusions in dementia is approximately 25%, whereas for hallucinations it is 10% to 15% [44]. Rather than systemized delusions, dementia patients tend to have isolated paranoid beliefs. For example, when they lose a wallet because of their memory impairment, they might become convinced that it was stolen and persist in this belief despite evidence to the contrary. Among dementia patients, visual hallucinations are also more common than auditory hallucinations, particularly in dementia of Lewy bodies [45]. Hallucinations associated with dementia often involve seeing familiar people, including those who are deceased, which may not be distressing to the patients.

Similar to the treatment of depression associated with dementia, behavioral interventions for psychotic symptoms are available, but not practical in the ICU setting. Distraction techniques and avoiding arguments are often helpful, but pharmacologic interventions might become necessary. Neuroleptics are effective in reducing hallucinations and delusions in dementia patients, but because of safety concerns associated with increased stroke and transient ischemic episode risk in dementia patients, the US Food and

Table 2
Common antidepressant medications in mild cognitive impairment and dementia

Medication	Initial daily dose	Target daily dose	Notable adverse events	Comments
Fluoxetine	10 mg	20–40 mg	Restlessness Gastrointestinal distress Hyponatremia (SIADH)	Long half-life
Sertraline	25 mg	100–150 mg	(same as above)	
Citalopram	10 mg	20–40 mg	(same as above)	Minimal drug-drug interactions
Paroxetine	10 mg	20–40 mg	(same as above) Sedation Anticholinergic effects	
Bupropion	75 mg	150–300 mg	Seizure (rare)	Tends to be stimulating
Mirtazapine	7.5 mg	7.5–30 mg	Sedation	Sometimes used as a hypnotic
Trazodone	25 mg	50 mg	Orthostatic hypotension Priapism Sedation	Usually used as a hypnotic
Venlafaxine	37.5 mg	75–150 mg	Restlessness Gastrointestinal distress Hyponatremia (SIADH) Hypertension at high dose	Tends to be stimulating
Duloxetine	20 mg	30–60 mg	Restlessness	Also indicated for diabetic neuropathy
			Gastrointestinal distress	Likely useful in a variety of comorbid pain syndromes
			Hyponatremia (SIADH)	

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.

Drug Administration added a "black box" warning for their use in patients with dementia [46]. Other side effects to consider include sedation; medication-induced parkinsonism; metabolic syndrome; and orthostatic hypotension, to which frail elderly patients with dementia are particularly vulnerable. At low doses (eg, 0.25–1 mg of risperidone daily; 2.5–5 mg of olanzapine daily; 12.5–50 mg of quetiapine daily), however, these medications are tolerable and effective in treatment of psychotic symptoms in dementia. The decision to initiate neuroleptic treatment involves careful consideration and an open discussion with the patient and family regarding the potential benefits of treatment of hallucinations or delusions versus the potential risk for side effects [47]. Close monitoring for response and medication side effects is indicated. Table 3 lists common antipsychotics and their recommended dosage for treatment of psychosis in patients with MCI or dementia.

Agitation and aggression

Agitated behaviors, such as irritability, yelling, restlessness, and physical aggression, are common in dementia with an estimated prevalence of 20%

Table 3
Common antipsychotic medications for patients with mild cognitive impairment or dementia

Medication	Initial daily dose	Target daily dose	Adverse events	Comments
Risperidone	0.25 mg	0.25–1 mg	EPS, elevated prolactin level	Available as orally disintegrating tablet At doses $\geq$ 6 mg, EPS similar to conventional antipsychotics
Quetiapine	25 mg	25–100 mg	Sedation	Low incidence of EPS
Olanzapine	2.5 mg	2.5–10 mg	Sedation Weight gain Diabetes mellitus	Available in an intramuscular injection and as orally disintegrating tablet
Haloperidol	0.25 mg	0.25–2 mg	EPS	Conventional antipsychotic
			Dystonic reactions	Available as liquid and intramuscular formulations
Fluphenazine	0.25 mg	0.25–2 mg	EPS	Conventional antipsychotic
			Dystonic reactions	Available as liquid and intramuscular formulations

Abbreviations: EPS, extrapyramidal symptoms; SIADH, syndrome of inappropriate antidiuretic hormone.

to 25% [44]. Clinicians should keep in mind that agitation is a nonspecific phenomenon with a broad differential diagnosis. The most common etiologies for such behaviors include medical illnesses (eg, urinary tract infection, pneumonia); delirium; environmental stressors; psychiatric disorders (eg, depression psychosis); and the underlying dementia itself. The treatment of agitation and aggression depends on the underlying cause of the behavior (eg, depression, delirium, pain). If no underlying etiology beside dementia is apparent and the agitation or aggression is severe, empiric use of neuroleptics can be considered (eg, 0.25–1 mg of risperidone daily; 2.5–5 mg of olanzapine daily; 12.5–50 mg of quetiapine daily).

An alternative to atypical antipsychotic agents may be the acetylcholinesterase inhibitors and memantine. Several studies have shown these agents may help stabilize cognitive and behavioral problems in demented patients [45]. The reported efficacy among these agents varied, with the greatest positive effects seen with donepezil, which also has the greatest number of studies [48]. Other agents, such as the mood stabilizers valproic acid and carbamazepine, have been helpful. Anticonvulsants are useful second-line treatments with possible efficacy noted for valproic acid [49,50] and carbamazepine [51].

Benzodiazepines can be very effective in maintaining patient and staff safety in a behavioral emergency, but can exacerbate cognitive impairment.

Their use in the ICU setting should be kept to a minimum. Lorazepam is a benzodiazepine with the particular advantage of being available for both intravenous and intramuscular use, and a dose of 0.25 to 0.5 mg is often effective in such emergencies. Midazolam is an ultra-short-acting benzodiazepine whose use is usually restricted to critical care settings, which can be similarly useful if intravenous access is available.

Clinicians should keep in mind that one of the most overlooked and undertreated causes of agitation associated with dementia is pain [52]. It would be most unfortunate if a dementia patient with agitation from unrecognized pain is given neuroleptic medication that not only fails to address the underlying problem, but can place the patient at risk for side-effects associated with this type of medication.

Catastrophic reactions

A catastrophic reaction is a sudden, out-of-proportion expression of negative emotion (eg, sadness, frustration, anxiety, anger) that is precipitated by an environmental event or an interaction with someone (eg, family, medical staff) [8]. Such reactions often have little warning in a patient who otherwise has appeared calm and content, and they are typically time-limited. Catastrophic reactions can sometimes be associated with physical aggression. These episodes can be frightening for the patient, and for caregivers and staff.

Given that catastrophic reactions are usually time-limited events, reassurance and a calm demeanor by the clinician and staff is generally sufficient. In cases of severe episodes, a low dose of an as-needed medication may be helpful during the acute crises. Potential pharmacotherapy interventions include lorazepam (0.25–0.5 mg); risperidone (0.25–0.5 mg); quetiapine (12.5–50 mg); and trazodone (25–50 mg). Precipitants for the catastrophic reaction should be identified to avoid future recurrence.

Other behavioral symptoms

Cognitive impairment is the most common and apparent psychologic symptom of dementia. Four cholinesterase inhibitors (ie, tacrine, donepezil, rivastigmine, and galantamine) are approved for treatment of mild-to-moderate dementia caused by Alzheimer's disease. Given that the benefit of cholinesterase inhibitors or memantine (an *N*-methyl-D-aspartate receptor antagonist agent approved for the treatment of Alzheimer's disease) to the long-term progression of dementia has not been shown conclusively, however, ICU clinicians should not feel compelled to start them during the acute medical management. All cholinesterase inhibitors carry risk of increased gastric acid secretion, nausea, vomiting, and diarrhea. Cholinesterase inhibitors, less commonly, can cause muscle cramps, bradycardia, or exacerbations of asthma. It is reasonable to stop cholinesterase inhibitors when dementia patients are admitted to the ICU.

Apathy is often mistaken for depression in patients with dementia. Apathetic patients often show diminished volition, low self-motivation, low vitality, diminished emotions, and decreased goal-directed behavior. Unlike depressed patients, apathetic patients usually are not distressed, but appear contented. Psychostimulants (eg, methylphenidate), activating antidepressant agents (eg, bupropion), and amantadine have been shown to be beneficial, but in the ICU specific treatment is unlikely to be necessary.

Summary

With an aging population and longer life expectancy, the incidence of MCI and dementia is expected to increase in society. This vulnerable, elderly population with cognitive impairments is likely to be afflicted with medical problems requiring acute hospitalization, often in ICUs. A substantial proportion of patients with pre-existing cognitive impairments, such as dementia and MCI, are vulnerable to delirium and frequently suffer from noncognitive, behavioral symptoms. ICU physicians should become vigilant in recognizing pre-existing cognitive impairments to prevent delirium and to aid in the management of neuropsychiatric symptoms associated with dementia. Successful detection and management of noncognitive, behavioral symptoms associated with dementia in ICU leads to improved delivery of life-saving critical care to elderly patients.

References

[1] US Census Bureau. Current population reports, series P23–209, sixty-five plus in US: 2005. Available at: www.census.gov. Accessed March 6, 2008.
[2] Alzheimer's Association. Alzheimer's facts and figures, 2007. Available at: www.alz.org. Accessed March 6th, 2008.
[3] Chelluri L, Pinsky MR, Donahoe MP, et al. Long-term outcome of critically ill elderly patients requiring intensive care. JAMA 1993;269:3119–23.
[4] Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100: 1619–36.
[5] Angus DC, Kelley MA, Schmitz RJ, et al. Caring for the critically ill patient: current and projected workforce requirements for care of the critically ill and patients with pulmonary disease; can we meet the requirements of an aging population? JAMA 2000;284:2762–70.
[6] Erkinjuntti T, Wikstrom J, Palo J, et al. Dementia among medical inpatients: evaluation of 2000 consecutive admissions. Arch Intern Med 1986;146:1923–6.
[7] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. American Psychiatric Association: Washington, DC; 1994.
[8] Rabins P, Lyketsos CG, Steele CD. Practical dementia care. New York: Oxford University Press; 1999.
[9] Fox N, Warrington E, Seiffer A, et al. Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease: a longitudinal prospective study. Brain 1998;121:1631–9.
[10] Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.

[11] Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet 1997;349:1793–6.
[12] Tierney MC, Szalai JP, Snow WG, et al. Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. Neurology 1996;46:661–5.
[13] Bowen J, Teri L, Kukull W, et al. Progression to dementia in patients with isolated memory loss. Lancet 1997;349:763–5.
[14] Pisani MA, McNicoll L, Inouye SK, et al. Cognitive impairment in the intensive care unit. Clin Chest Med 2003;24:727–37.
[15] Fields SD, MacKenzie CR, Charlson ME, et al. Cognitive impairment: can it predict the course of hospitalized patients? J Am Geriatr Soc 1986;34:579–85.
[16] Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29(7):1370–9.
[17] McNicoll L, Pisani MA, Zhang Y, et al. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003;51(5):591–8.
[18] Pisani MA, Murphy TE, Van Ness PH, et al. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med 2007;167(15):1629–34.
[19] Inouye SK. Delirium in older persons. N Engl J Med 2006;354(11):1157–65.
[20] Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32(4):955–62.
[21] Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27(12):1892–900.
[22] Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–62.
[23] Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42(8):809–15.
[24] O'Keeffe ST, Lavan JN. Predicting delirium in elderly patients: development and validation of a risk-stratification model. Age Ageing 1996;25(4):317–21.
[25] Litaker D, Locala J, Franco K, et al. Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 2001;23(2):84–9.
[26] Ljubisavljevic V, Kelly B. Risk factors for development of delirium among oncology patients. Gen Hosp Psychiatry 2003;25(5):345–52.
[27] Rothschild JM, Leape LL, Smith AH. The nature and extent of medical injury in older patients: executive summary. Washington, DC: AARP Public Policy Institute; 2000.
[28] Roca RP, Klein LE, Kirby SM, et al. Recognition of dementia among medical patients. Arch Intern Med 1984;144:73–5.
[29] Pisani MA, Redlich C, McNicoll L, et al. Under-recognition of pre-existing cognitive impairment by physicians in older ICU patients. Chest 2003;124:2267–74.
[30] Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. Ann Intern Med 1995;122:422–9.
[31] Valcour VG, Masaki KH, Curb JD, et al. The detection of dementia in the primary care setting. Arch Intern Med 2000;160:2964–8.
[32] Ardern M, Mayou R, Feldman E, et al. Cognitive impairment in the elderly medically ill: how often is it missed. Int J Geriatr Psychiatry 1993;8:929–37.
[33] Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859–64.
[34] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3):189–98.
[35] Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797–811.

[36] Jorm AF, Scott R, Cullen JS, et al. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. Psychol Med 1991;21: 785–90.
[37] Pisani MA, Inouye SK, McNicoll L, et al. Screening for pre-existing cognitive impairment in older intensive care unit patients: use of proxy assessment. J Am Geriatr Soc 2003;51(5): 689–93.
[38] Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the Cardiovascular Health Study. JAMA 2002; 288:1475–83.
[39] Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: the Cache County Study. J Neuropsychiatry Clin Neurosci 2003;15: 340–5.
[40] Steinberg M, Tschanz JT, Corcoran C, et al. The persistence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 2004;19:19–26.
[41] Chan DC, Kasper JD, Black BS, et al. Prevalence and correlates of behavioral and psychiatric symptoms in community-dwelling elders with dementia or mild cognitive impairment: the Memory and Medical Care Study. Int J Geriatr Psychiatry 2003;18(2):174–82.
[42] Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry 2002;52(3):243–52.
[43] Olin JT, Katz IR, Meyers BS, et al. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. Am J Geriatr Psychiatry 2002;10(2):129–41.
[44] Lyketsos CG, Steinberg M, Tschanz JT, et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on memory in aging. Am J Psychiatry 2000;157: 708–14.
[45] Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. Am J Psychiatry 2007;164(10):1491–8.
[46] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294: 1934–43.
[47] Jeste DV, Blazer D, Casey D, et al. ACNP white paper: update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 2008;33(5):957–70.
[48] Miller LJ. The use of cognitive enhancers in behavioral disturbances of Alzheimer's disease. Consult Pharm. 2007;22:754–62.
[49] Profenno LA, Jakimovich L, Holt CJ, et al. A randomized, double-blind, placebo-controlled pilot trial of safety and tolerability of two doses of divalproex sodium in outpatients with probable Alzheimer's disease. Curr Alzheimer Res 2005;2(5):553–8.
[50] Tariot PN, Raman R, Jakimovich L, et al. Valproate Nursing Home Study Group. Divalproex sodium in nursing home residents with possible or probable Alzheimer disease complicated by agitation: a randomized, controlled trial. Am J Geriatr Psychiatry 2005;13(11): 942–9.
[51] Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998;155(1):54–61.
[52] Parmalee PA. Pain in cognitively impaired older persons. Clin Geriatr Med 1996;12(3): 473–87.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 737–765

CRITICAL
CARE
CLINICS

Neurobehavioral Management of Traumatic Brain Injury in the Critical Care Setting

David B. Arciniegas, MD[a,b],
Thomas W. McAllister, MD[c,*]

[a]*Brain Injury Rehabilitation Unit, HealthONE Spalding Rehabilitation Hospital, 900 Potomac Street, Aurora, CO 80011, USA*
[b]*Neurobehavioral Disorders Program, Department of Psychiatry, University of Colorado School of Medicine, Campus Box C268-25, 4200 East 9th Avenue, Denver, CO 80262, USA*
[c]*Section of Neuropsychiatry, Department of Psychiatry, Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, NH 03756, USA*

Critical care professionals are increasingly involved in the early post-injury management of individuals hospitalized after a traumatic brain injury (TBI). Approximately 230,000 persons in the United States experience a TBI-associated hospitalization annually [1,2], the majority of which are acquired through injuries involving transportation, falls, assaults, or firearms. Adolescents, young adults, and older persons are overrepresented among persons hospitalized who have TBI, as are persons who have moderate or severe injuries [1,2]. Although the overall rate of TBI-associated hospitalization declined 51% between the early 1980s and late 1990s [1,2], that decline largely is attributable to reductions in hospital-based care of mild and moderate TBI (−61% and −19%, respectively). An absolute increase of 90% in hospitalization rates after severe TBI (from 10 to 19 per 100,000 persons per year) occurred during this same time. Concurrently, in-hospital TBI mortality rates declined 17%. Improvements in trauma care, pre- and in-hospital, are cited as among the most important factors contributing to the increased numbers of persons with severe TBI presenting to hospitals despite absolute reductions in TBI-associated hospitalizations,

This work was supported in part by the National Institutes of Health (grants RO1 NS40472-01, RO1 HD048176-01, RO1 NS055020, and R01HD48638), the New Hampshire Hospital, the Ira DeCamp Foundation, and HealthONE Spalding Rehabilitation Hospital.

* Corresponding author.
E-mail address: thomas.w.mcallister@dartmouth.edu (T.W. McAllister).

doi:10.1016/j.ccc.2008.06.001

and also to improvements in post-TBI survival [1,2]. This trend also indicates that many individuals now present to hospital with and survive TBI despite severities of injury that in years past often would have been fatal.

Among those hospitalized after a moderate or severe TBI, approximately 35% (or approximately 80,500 persons annually) are expected to develop permanent disability as a result of that TBI [2,3]. Posttraumatic physical, cognitive, and behavioral impairments, denoted collectively by the term, *neurobehavioral*, are particularly common among persons who have severe TBI [4–8]. The neurobehavioral sequelae of TBI contribute substantially to postinjury disability [9–11] and present substantial challenges for patients and their families during and after the early postinjury period [10,12–14].

The care provided to persons who have TBI in critical care settings, to the authors' knowledge, rarely is framed as neurobehavioral. Given the potential for loss of life and severe medical or neurologic compromise in the acute postinjury period, the focus on such matters in the critical care setting is understandable and necessary. There is no doubt, however, that the initial treatment of posttraumatic neurobehavioral disturbances also begins in the emergency department (ED) and critical care unit (CCU). Identifying and treating neurobehavioral disturbances and avoiding interventions with the potential for acute or long-term neurobehavioral complications are essential if improvements in long-term neurobehavioral outcomes from TBI are to be achieved. Accordingly, developing critical care professionals' expertise in the neurobehavioral management of TBI is an important objective. In the service of this objective, this article begins by defining TBI, including its several subtypes and severities, and reviewing the commonly used methods of identifying and characterizing TBI in the critical care setting. The neurobiology of TBI, including neuroanatomy, neurochemistry, and brain-behavior relationships, relevant to the management of acute postinjury neurobehavioral problems is described. Finally, recommendations regarding the management of posttraumatic neurobehavioral problems in the critical care setting are offered.

Defining and characterizing traumatic brain injury

General clinical case definition

Consistent with the *Guidelines for Surveillance of Central Nervous System Injury* developed by the United States Centers for Disease Control and Prevention [15], TBI is defined as a functionally significant disruption of brain function manifested as immediately apparent cognitive or physical impairments that result from blunt or penetrating trauma or rapid acceleration or deceleration forces. This definition excludes lacerations or contusions of the face, eye, or scalp, and fractures of facial bones alone as evidence of TBI. Additionally, injury to the brain resulting from birth trauma, hypoxic-ischemic (anoxic), inflammatory, toxic, or metabolic encephalopathies,

primary ischemic or hemorrhagic strokes, seizure disorders, intracranial surgery, and cerebral neoplasms also are outside the definition of TBI.

Although the standard clinical case definition used in federally funded central nervous system injury surveillance programs permits skull fracture alone as evidence sufficient to merit a diagnosis of TBI, this article uses a definition that requires evidence of brain dysfunction even if skull fracture is present; although skull fracture is associated with an increased likelihood of intracranial (cerebral) injury [16–18], it is not a sufficiently reliable predictor of such injury to serve as the sole clinical finding with which to diagnose TBI [19]. Thus, use of *head injury* as a synonym for TBI is discouraged and is not used herein.

Under this definition of TBI, no single symptom or sign (eg, loss of consciousness, altered mental status, or subdural hematoma) is pathognomonic of TBI. The definition of TBI also does not specify the duration of disrupted brain function produced. The *Guidelines* define clearly the data elements necessary to describe the occurrence and severity of TBI (Table 1) [15], but interpreting those data with respect to rendering a diagnosis of TBI is left to the judgment of clinicians.

Characterizing severity of traumatic brain injury in the critical care setting

TBI severity is divided into three categories: mild, moderate, and severe. The Glasgow Coma Scale (GCS) [20] is the measure used most commonly in the ED and CCU to determine TBI severity, with mild, moderate, and severe TBI defined by GCS scores 13–15, 9–12, and 3–8, respectively. On admission and throughout the initial hospitalization, interpretation of GCS scores requires contextualization: intoxication with illicit or prescribed agents, severe facial trauma, language barriers, and other premorbid conditions (eg, severe developmental disabilities or advanced dementia) at the time of GCS assessment may lower performance on this measure and provide potentially misleading information regarding TBI severity. Additionally, although it is common practice in critical care settings to qualify the GCS score among intubated patients by placing a 'T' next to their score (eg, GCS 3T), the clinical and predictive validity of such qualified GCS scores is not established clearly. Such caveats [21] regarding the interpretation and limitations of GCS scores notwithstanding, GCS assessment on ED presentation and serially (at least once every 24 hours) throughout the critical care period provides immediately relevant information about patient clinical status and prognosis [6,22,23]. Exceptions to this rule are patients who have GCS scores in the 13–15 range and abnormal CT or MRI; outcomes in these patients resemble those of persons who have moderate TBI and, hence, are designated as complicated mild TBI [24,25]. In these cases, the neurologic and neurobehavioral treatment needs and prognostic implications require considerable attention despite GCS scores that are, at face value, in the mild range.

Table 1
Conditions and the evidence that may be used to substantiate the occurrence of TBI

Conditions suggesting traumatic brain injury	Evidence suggestive of the condition
Decreased level of consciousness (observed or self-reported)	Alteration or complete loss of consciousness, including states described as obtundation, stupor, or coma
Amnesia	Loss of memory for events immediately preceding an injury (retrograde amnesia), for the injury or the events that follow it (anterograde amnesia), or both
Objective neurologic abnormality	Motor (including speech), sensory, or reflex abnormalities evident on neurologic examination and/or the occurrence of seizures
Objective neuropsychologic abnormality	On mental status (including standardized neuropsychological) examinations, there is evidence of impairment in cognition (eg, disorientation or confusion), disturbances of behavior (eg, agitation), or other abnormalities in neuropsychiatric status (eg, personality change)
Diagnosed intracranial lesion	By CT, MRI, or other neurodiagnostic test, there is evidence of diffuse axonal injury; epidural, subdural, subarachnoid, or intracerebral hematoma; cerebral contusion or laceration; or penetration of brain by a foreign body (eg, gunshot wound)

Data from Marr AL, Coronado VG. Central nervous system injury surveillance data submission standards—2002. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention National Center for Injury Prevention and Control; 2002.

Even when GCS scores are available, assessing TBI severity by the duration of posttraumatic amnesia (PTA) also is suggested. PTA describes the period of dense impairment in the ability to learn new information (with or without some degree of retrograde amnesia) and is best assessed using one of the several currently available PTA scales [26–30]. Among these, the authors recommend the Orientation Log (O-Log) for use in the CCU [31]. In keeping with the definition of mild TBI offered by the American Congress of Rehabilitation Medicine (ACRM) [32], PTA duration of less than 24 hours is consistent with mild TBI. Russell and Smith (1961) [33], progenitors of the concept and assessment of PTA, suggested additional categories of severity beyond 24 hours defined by PTA durations of 1 to 7 days and more than 7 days. In view of the ACRM definition, these durations of PTA would now serve most usefully as cutoffs for moderate and severe TBI, respectively. Regardless of the cutoffs used to define categories of TBI severity, PTA duration (as a continuous variable) is a robust predictor of functional independence [30,31,34] and disability [34] at the end of acute inpatient rehabilitation, Glasgow Outcome Scale [35] scores at 6- and 12-months post injury [36,37], long-term cognitive recovery [38–40],

productivity [41], employment [42], and community reintegration [43]. As with the GCS, noninjury factors (sedating medications, severe communication impairments, and so forth) may confound assessment of PTA duration. Nonetheless, including serial examination using the O-Log or another measure of PTA—at the earliest point after TBI at which a patient is capable of participating in such examinations—is recommended strongly as a means by which to characterize not only injury severity but also to develop prognostic formulations and guide treatment planning.

Neurobiology of traumatic brain injury

Developing a rational approach to the neurobehavioral management of persons who have TBI in the critical care setting requires familiarity with the neuroanatomy and neurochemistry of this condition. As described later in this section, the neurobiology of TBI not only predicts the neurobehavioral problems that arise commonly in the early postinjury period but also informs treatment selection (agents to use and those that are best avoided). The neurobiological bases of TBI are grouped broadly into several categories: biomechanical injury, cytotoxic injury, and secondary or systemic complications with effects on the brain. Blast-related injury is another possible category of TBI and is discussed briefly.

Biomechanical injury

The biomechanical effects of nonpenetrating injuries may be divided broadly into two types, both of which usually are operative in severe TBI: contact and inertial. Contact injuries result when the brain, moving inside the skull, strikes the inner surface of skull or is struck by material (eg, projectiles or bone fragments) entering the intracranial space. In the former circumstance, movement of brain against the various ridges and bony protuberances of the anterior (frontal) and middle (temporal) fossas is particularly injurious to the temporal and frontal poles and the ventral anterior, medial, and lateral temporal and frontal cortices [44–48]. In the latter form of contact injury, tissue displacement or destruction by a projectile; fragmentation and deposition of bone or a projectile within brain tissue; contamination of the intracranial space by potential infectious material on a projectile or the tissues through which it passes; subarachnoid, subdural, or epidural hematomas; and other process contribute to the brain injury.

Linear translation and rotational forces, which in combination produce angular acceleration or deceleration, can result in straining, shearing, and compression of brain tissue [49–55]. Strain and shear forces are tolerated poorly by brain tissue; when these forces exceed the tolerances of brain tissue, TBI is produced. These forces tend to be maximal in brain areas that experience the highest angular acceleration or deceleration forces (superficial > deep and anterior > posterior), at the planes between tissues

of different densities and elasticities (eg, junction between gray and white matter), and at the rotational center of mass in the intracranial space (rostral brainstem). The effects of high-speed, long-duration acceleration or deceleration injuries are maximal on axonal projections and small blood vessels within and from the brainstem, the parasagittal white matter of the cerebrum, the corpus callosum, the gray-white junctions of the cerebral cortex [56], and especially at gray-white junctions in the ventral and anterior frontal and temporal lobes [44]. Although injury to axons produced by inertial injury usually is described as diffuse axonal injury, this term, despite its well-accepted use in the TBI literature, is a misnomer: regional differences in susceptibility to the effects of inertial forces results in pattern that is described more appropriately as multifocal rather than diffuse [56].

Nonpenetrating and penetrating traumatic brain injury

Nonpenetrating injuries comprise the vast majority of TBI; are most commonly sustained through motor vehicle accidents, falls, and assaults; and disproportionately involve adolescents, young adults, and older persons [2]. Across nonpenetrating TBI at all levels of severity, inertial forces are the principal drivers of the pathophysiology of TBI and diffuse axonal injury is the primary consequence [56–58]. In more severe TBI, contact injuries also occur and produce focal injuries in the patterns described in the preceding section of this article.

Penetrating TBI refers to contact injury to the brain produced by objects entering the intracranial space. In the United States, penetrating injuries represent the minority (approximately 10%) of TBI, generally are caused by firearms (also approximately 10% of all TBI), frequently are fatal (90%), and often are self-inflicted (67%) [2]. The damage sustained in penetrating injuries is predominantly focal, involving the path through which an object travels within the brain. Although the effects of inertial forces imparted by a missile on the skull or brain may play a role in the pathophysiology of penetrating TBI [59], this type of injury tends to be stroke-like with regard to its focal effects on the brain and the posttraumatic neurobehavioral deficits and outcome with which it is associated. Although penetrating injuries are not excluded from consideration in the remainder of this article, the material presented herein is more immediately relevant to nonpenetrating TBI.

Cytotoxic injury

Injurious cytotoxic processes are initiated by biomechanical injury, and these add to and complicate TBI (see Povlishock and Katz [57] and Bigler [60] for review). Injury-induced calcium and magnesium dysregulation, free radical formation, and excitatory amino acid and neurotransmitter disturbances (reviewed by Arciniegas and Silver [61]) are major elements of the

postinjury cytotoxic cascade that contribute to neuronal injury and cell death.

Excesses of excitatory amino acids (ie, glutamate) result in an influx of calcium into neurons that produces neuronal depolarization, initiates oxidative processes, activates proteolytic enzymes, and ultimately injures or destroys the neuron or its axonal terminus [56,60]. Additionally, glutamate excesses drive glucose use, oxidative metabolism, and the production of potentially toxic accumulations of lactate [62,63]. Cholinergic excesses also seem to be excitotoxic, may amplify the destructive effects of excitatory amino acid excesses, and may be particularly injurious to brain areas where acetylcholine and excitatory amino acids are densely co-located (ie, hippocampus and frontal cortices) [64].

The effects of cerebral monoaminergic excesses in the cytotoxic cascade are not understood fully, although in experimental injury models traumatically induced elevations of cerebral serotonin seem to decrease cerebral glucose use (possibly counterposing the effects of glutamate) [65,66]. Consistent with this observation, serotonin-augmenting agents administered in the acute period after severe TBI do not improve posttraumatic neurobehavioral status or TBI outcome [67,68]. Administration of catecholamine antagonists impedes recovery from brain injury [69–71] and delay emergence from PTA in humans [72], suggesting that blocking catecholamine excesses is not an effective means by which to mitigate the cytotoxic cascade after TBI.

Neurotransmitter excesses seem to wane over the first several weeks after TBI [73,74], although the time course of their resolution is not characterized fully. TBI in humans produces chronic cerebral cholinergic deficit via injury to ventral forebrain cholinergic nuclei [75,76] and their cortical projections [76–78]. It is possible that TBI also results in primary or secondary disturbances in monoaminergic systems [79], the effects of which may be amplified by individual genetically mediated variations in catecholamine metabolism [80]. There is a substantial body of evidence suggesting roles for cholinergic or catecholaminergic augmentation in the remediation of posttraumatic impairments in attention and memory [61,79,81,82]. These interventions generally have been studied in the subacute or late postinjury period, however, with few exceptions [83,84], leaving their role in the management of posttraumatic neurobehavioral disturbances in the critical care setting uncertain.

Secondary and systemic complications

Biomechanical and cytotoxic injury processes may occur without medical or neurological complication; however, such complications may occur frequently particularly in the setting of severe TBI. Among the more common of these secondary processes are traumatic hematomas (eg, subdural, epidural, subarachnoid, and intraparenchymal hematomas). Other common

secondary neurologic complications of TBI include focal or diffuse cerebral edema, elevated intracranial pressure (ICP), obstructive hydrocephalus, hypoxic-ischemic injury, and infection (particularly with the introduction of foreign material into the intracranial space). Less commonly, or when these processes are unable to be well controlled, subfalcine or transtentorial herniation may occur. Even when not fatal, such herniations may compromise vascular supply, resulting in stroke superimposed on TBI. Because TBI frequently occurs in the context of other injuries (polytrauma), other systemic medical complications, such as volume depletion or blood loss, hypoperfusion, hypo- or hyperthermia, hypoxia, infection, and related problems, commonly are comorbid with TBI. Their occurrence may further compromise a patient's neurologic status and increase posttraumatic mortality and morbidity; aggressive treatment directed at these problems, therefore, is essential [85].

Blast-related traumatic brain injury

In addition to the biomechanical and cytotoxic injury processes and secondary and systemic complications contributing to penetrating and nonpenetrating TBI, increasing attention has been given recently to the possibility of a third basic category of TBI: blast injury [86–93]. The combination of effective overpressure and positive pulse duration may effect injury through primary (blast wave), secondary (objects displaced by the blast striking or penetrating the body or brain), tertiary (body or brain displaced by blast striking objects or ground), and quaternary or miscellaneous means [91,94–96]. Quaternary or miscellaneous injury refers to burns, exposure to toxic gases and dust, hypoxia resulting from airway compromise or toxic exposure, structural collapse, body rupture, and psychologic trauma associated with the blast event. Experimental injury studies [97–102] suggest that blast forces may injure the brain and brainstem via afferent hyperexcitability, increased neurotransmitter and vasoconstrictor or vasodilator autacoid release, or kinetic energy transfer of blast overpressure to the brain. Others [103–105] note that blast exposure induces the vagally mediated pulmonary defensive reflex, resulting in blast-related shock even in the absence of overt external injury; it is possible, therefore, that the clinical phenomena attributed to TBI (eg, being ''stunned'' by a blast and alterations or loss of consciousness) in some cases may reflect the occurrence of this vagally mediated reflex rather than direct disruption of brain physiology by primary blast forces. In light of the uncertain effects of primary blast on the central nervous system, particularly in the setting of blast exposures that fail to injure hollow organs (which are at greatest risk for injury due to primary blast), it may be most accurate to refer to TBI in the setting of blast exposure as blast-related TBI. This term encompasses broadly and fairly the spectrum of primary, secondary, tertiary, and miscellaneous (especially hypoxic and psychologic) mechanisms that operate concurrently in blast exposures and

by which injury to the brain and post-blast neurobehavioral disturbances may be produced.

Neurobehavioral sequelae of traumatic brain injury in the critical care setting

The biomechanical and cytotoxic processes induced by severe TBI disproportionately affect the anterior and ventral aspects of the frontal and temporal lobes, medial frontal and temporal areas, ventral forebrain, the diencephalon (thalamus and hypothalamus), the rostral and ventral areas of the upper brainstem, and the white matter within and between these areas [44,56,57,60,75,106–108]. These are neurobehaviorally salient areas, and their injury results in predictable types of posttraumatic neurobehavioral disturbances (Table 2). Patients sometimes present with a single focal neurobehavioral deficit after TBI, although this is seen more often after penetrating rather than nonpenetrating TBI. Among persons who have moderate or severe nonpenetrating TBI, neurobehavioral disturbances arise in reasonably consistent (although not invariate) combinations and usually evolve in a predictable manner during the postinjury period. The term, *posttraumatic encephalopathy (PTE)*, captures this broad spectrum of TBI-induced neurobehavioral disturbances seen in the critical care setting.

The authors, in clinical work and research in the early postinjury period, find it useful to divide PTE into five stages: posttraumatic coma, posttraumatic delirium, PTA, posttraumatic dysexecutive syndrome, and recovery. These stages are named according to the most salient (although not the only) neurobehavioral feature of the clinical presentation: coma, a complete impairment of arousal; delirium, an alteration in arousal, profound inattention, with or without agitation or aggression; amnesia, a dense impairment in new learning; dysexecutive function, a constellation of impairments in higher-level attention, memory, and other cognitive functions; and recovered neurobehavioral health. These stages parallel those described by the Rancho Los Amigos Levels of Cognitive Functioning Scale (RLAS) (Table 3), one of the more commonly used methods of characterizing and staging TBI recovery in rehabilitation settings [109,110].

The impairments that comprise each stage occur on a continuum, which makes drawing clear distinctions between the PTE and RLAS stages difficult when working with specific patients. Nonetheless, identifying the stage of PTE that best describes a patient is useful: it facilitates the development of a treatment plan that is appropriate to a patient's current clinical status and that anticipates the course of spontaneous and treatment-facilitated recovery. As a corollary to this thesis, identifying the stage of PTE also helps identify deviations from the expected course of recovery and, hence, the need to evaluate patients for neurologic, neuropsychiatric, and medical problems responsible for such deviations.

Table 2
Brain-behavior relationships relevant to understanding the neurobehavioral sequelae of traumatic brain injury commonly encountered in the critical care setting

Structure	Neurobehavioral function	Consequence of injury
Rostral and ventral brainstem		
Reticulothalamic system (predominantly ACh, Glu, GABA)	Arousal	Partial or complete impairment
Reticulocortical system (DA, NE, 5-HT, ACh)	Arousal, attention, facilitation of cortical readiness for information processing	Diminished arousal, attention, inability to engage effectively in information processing
Thalamus		
Reticulothalamic system	As above	As above
Thalamo-cortico-thalamic circuits (predominantly Glu, GABA)	Subnuclei cross-link cortical and subcortical areas	Impaired information processing within the sensory, motor, or neurobehavioral domain served by the affected thalamic area
Hypothalamus	Multiple subnuclei involved in autonomic, neuroendocrine, circadian, and some primitive social functions	Autonomic dysfunction, impaired thermoregulation, impaired feeding behaviors, endocrine abnormalities (including panhypopituitary presentations), altered sleep-wake cycles, pathologic laughter or anger
Ventral forebrain	Cholinergic supply to medial temporal and neocortical areas	Impaired information processing in multiple cognitive domains, in particular attention, memory, and executive functions
Medial temporal areas		
Entrorhinal-hippocampal complex	Preattentive information filtering (sensory gating), declarative memory; also contributes to other attention and working memory processes	Impairments in attention, working memory and declarative memory (who, what, when, and where)
Amygdala	Generation of contextually relevant emotional and social behavior	Affective placidity, Klüver-Bucy–like syndromes
Ventral frontal cortices (straight gyrus, lateral orbitofrontal)	Social behavior, in particular restraint of primitive (limbic) behaviors	Impulsivity, social (including sexual) disinhibition, irritability, agitation, aggression

Medial frontal (anterior cingulate) cortex	Motivation	Decreased goal-directed cognition, emotion, and behavior (apathy)
Inferior (inferolateral) prefrontal cortex	Working memory	Impaired working memory
Dorsolateral prefrontal cortex	Executive function	Impairments in executive function (higher-level cognition) and executive control of attention, working memory, memory (retrieval), language, motor planning, and other basic cognitive functions
White matter	Connections between cortical areas, rapid information processing (myelinated fibers)	Interruption of neural networks serving cognition, emotion, and behavior, resulting in slowed and inefficient information processing

Abbreviations: 5-HT, serotonin; ACh, acetylcholine; DA, dopamine; GABA, γ-aminobutyric acid; Glu, glutamate; NE, norepinephrine.

Table 3
An overview of the stages of recovery from severe traumatic brain injury using the framework of posttraumatic encephalopathy and the Rancho Los Amigos Levels of Cognitive Functioning Scale

RLAS stage	Dominant features	Description	Posttraumatic encephalopathy stage
I	No response	A complete impairment of arousal with no response to sensory input and no spontaneous (purposeful or nonpurposeful) behavior; posttraumatic coma.	Posttraumatic coma
II	Generalized response	A partial impairment of arousal in which patients may appear alert but profoundly inattentive and nonpurposeful (severe hypoaroused posttraumatic delirium).	Posttraumatic delirium
III	Localized response	A partial but less severe impairment of arousal in which patients are awake, intermittently attentive to simple stimuli (people, objects, and stimulation), and may be able to follow some simple commands (moderately severe hypoaroused posttraumatic delirium).	Posttraumatic delirium
IV	Confused and agitated	Patients are alert but cognitively impaired and agitated. Severe impairments of attention, processing speed, working memory, declarative memory, functional communication, and executive function are present and denoted collectively as *confusion*. Restlessness or agitation is present, and aggression verbal or physical) may occur with little or no provocation (agitated posttraumatic delirium).	Posttraumatic delirium

V	Confused, inappropriate behavior but not agitated	Similar to stage IV but without prominent or frequent agitation or aggression and with improving ability to be engaged in examination or treatment. Memory impairment (PTA) is a salient feature of this stage; however, other cognitive impairments are present, impair patients' ability to organize behavior, and contribute to the continued appearance of confusion (mild posttraumatic delirium).	Resolving posttraumatic delirium or early PTA
VI	Confused but appropriate behavior	Similar to stage V but with improved ability to perform basic activities of daily living and to engage in examination or treatment. Substantial cueing/supervision/assistance with such tasks generally is needed (incompletely resolved posttraumatic delirium or early PTA).	PTA
VII	Automatic and appropriate behavior	Patients generally are able to perform basic self-care activities, and confusion no longer is present. Impairments in declarative memory, however, often are the most salient and problematic features of this stage of recovery (PTA), but functionally significant impairments in higher-level attention, working memory, and executive function (including insight) also are present.	Resolving PTA or early posttraumatic dysexecutive syndrome
VIII	Purposeful and appropriate behavior	Patients have emerged from PTA (the period of dense impairments in new learning) and are independent for basic self-care abilities and some higher-level activities of daily living. Higher-level impairments, however, in attention, working memory, declarative memory (retrieval), and executive function often persist (posttraumatic dysexecutive syndrome), and assistance or supervision for their performance generally is required.	Posttraumatic dysexecutive syndrome

Data from Hagen C, Malkmus D, Durham P. Rancho Los Amigos Scale. Communication Disorders Service, editor. Rancho Los Amigos Hospital; 1972.

Evaluating posttraumatic neurobehavioral disturbances

General considerations

A comprehensive assessment of the patient, including identification of relevant pre-injury medical, neurologic, psychiatric, and substance histories and thorough neurologic and neurobehavioral examinations are prerequisites to the evaluation and treatment of posttraumatic neurobehavioral disturbances. Comprehensive and ongoing neurologic and medical evaluation is standard care in the CCU, the guidelines for which are described elsewhere [85] and form the foundation on which subsequent assessment of posttraumatic neurobehavioral disturbances is predicated.

Among these neurologic and medical evaluations, several issues merit special mention. Bedside electroencephalographic monitoring in the early postinjury period is encouraged [111,112] for identification of posttraumatic (including nonconvulsive) seizures and as a method by which to distinguish between ictal or postictal and injury-induced alterations in consciousness or behavior. Vigilance for temporal relationships between alterations in mental status or behavior and minor medical problems (eg, urinary tract infection, metabolic disturbances, hypotension, hypoglycemia, and mild hypoxia) is needed: in a manner similar to that of many geriatric patients, the earliest manifestations of such problems in many persons who have moderate or severe TBI often are neurobehavioral. When new neurobehavioral problems develop or previously resolved ones recur, medical re-evaluation should be initiated before prescribing agents (where possible) to manage that neurobehavioral change or decline.

Other common sequelae of TBI and polytrauma (in particular headache, neck, back, or other sources of pain; dizziness; sleep disturbance; fatigue; and psychologic responses) may produce or exacerbate TBI-related neurobehavioral disturbances. Similarly, the high frequency of alcohol and substance use disorders among persons who have TBI [113] suggests the need to consider substance intoxication at the time of admission and substance (especially alcohol) withdrawal during the early hospitalization period in the differential diagnosis of posttraumatic neurobehavioral disturbances. When any of these problems are identified, treatment directed at them is necessary and may change the need for or selection of agents directed at PTE specifically.

Posttraumatic seizures and anticonvulsant agents

The management of posttraumatic seizures and the medications used to prevent their occurrence require special consideration in the differential diagnosis and treatment of posttraumatic neurobehavioral disturbances. As reviewed by Frey [114], persons who have moderate or severe TBI are at risk for posttraumatic seizures by virtue of the anatomy (frontal and temporal) and neurochemistry (especially excitotoxicity) of this condition.

Posttraumatic seizures generally are divided into early (within 1 week of injury) and late (after the first week postinjury) types. Administration of anticonvulsant medications (seizure prophylaxis) during the first week post TBI is associated with a decreased incidence of early posttraumatic seizures [115] and their use for this purpose is consistent with the evidence-based guidelines for traumatic brain injuries [85]. Reduction of early seizures does not reduce mortality, long-term neurologic disability, or the risk for late posttraumatic seizures [115]. Additionally, use of anticonvulsants after the first week post injury does not prevent the development of late posttraumatic seizures. Many of these agents, in particular phenytoin [116,117] and carbamazepine [117], are associated with treatment-related impairments in cognitive and motor function. Levetiracetam is gaining popularity as an agent for seizure prophylaxis in the critical care setting [118,119], but there are no randomized, controlled studies supporting its use for prophylaxis of early or late posttraumatic seizures. This agent also may increase the risk for agitation and other neurobehavioral disturbances [120,121], in particular among persons who have a history of psychiatric problems. Valproate seems to be benign with respect to its effects on cognition [122] and other neurobehavioral functions and for this reason is suggested as preferable, from a neurobehavioral perspective, to phenytoin, carbamazepine, and levetiracetam when prophylaxis against early posttraumatic seizures is undertaken. Continued use of any of these or other anticonvulsants, however, as prophylaxis against new-onset seizures after the first week post injury (ie, late posttraumatic seizures) is not recommended [85].

When early or late posttraumatic seizures (including nonconvulsive types) occur, identifying ictal and postictal alterations of consciousness or behavior directs treatment toward seizure control rather than the neurobehavioral disturbances per se. As discussed previously, valproate is preferred from a neurobehavioral perspective to phenytoin, carbamazepine, or levetiracetam for the treatment of early and late posttraumatic seizures.

Other medications that complicate neurobehavioral assessment and recovery from traumatic brain injury

There are a variety of potentially life-saving pharmacologic interventions provided to persons who have moderate or severe TBI in the ED and CCU that may complicate neurobehavioral assessment and possibly recovery from TBI. Some historically common practices are recognized as unnecessary or potentially harmful, for example the administration of corticosteroids for improving outcome or reducing posttraumatic ICP or routine administration of barbiturates for ICP management [85]. Other practices, such as analgesic or hypnotic-based sedation during mechanical ventilation, are common and necessary [123], but their effects on neurologic and neurobehavioral recovery after TBI remain uncertain or concerning. Critical care physicians and staff face difficult choices when selecting agents to assist with

mechanical ventilation, to provide adequate analgesia, or to control agitation among persons who have TBI. Accordingly, a proscriptive approach to pharmacotherapy in the critical care setting is not reasonable. It is prudent, however, to remain mindful of the potential to complicate neurobehavioral status or delay neurologic and neurobehavioral recovery after TBI by use of these types of medications and, therefore, to consider alternatives to them.

For example, antagonists of type-2 dopamine (D2) receptors or benzodiazepines commonly are used in for the treatment of agitation and delirium and as an adjunctive agent to improve compliance with mechanical ventilation [124]. Agents with noradrenergic-attenuating effects (eg, clonidine) sometimes also are used for these and other purposes. Animal models suggest, however, that dopamine and norepinephrine antagonists delay neuronal recovery and impair neuronal plasticity [69,70,125,126]. Among persons with TBI, typical antipsychotics exacerbate cognitive impairments [127] and may prolong the period of PTA [72]. Benzodiazepines are known to impair memory and other aspects of cognition [128] in healthy adults and seem to do so also among persons with TBI [129]. The cholinergic deficits resulting from TBI leave patients vulnerable to the adverse cognitive and behavioral effects of agents with anticholinergic properties [61,81]. Opiate analgesia produces impairments in memory among persons without TBI of severity comparable to those encountered among persons in PTA [130], suggesting a nontrivial risk for exacerbating or prolonging posttraumatic coma, posttraumatic delirium, or PTA as a result of their administration. Avoiding, eliminating, or using the minimum-necessary dose of any of these agents for as brief a time as is feasible clinically is encouraged. Discontinuing these medications also is necessary before drawing conclusions about the severity, prognosis, and the need for treatment of PTE and attendance neurobehavioral disturbances. Alternate medications for the management of posttraumatic neurobehavioral disturbances are discussed later.

Assessment of posttraumatic encephalopathy

The assessment of PTE is most usefully and accurately undertaken using standardized assessments appropriate to the phase of PTE in which patients present to the critical care setting. These types of assessments facilitate accurate diagnosis of the type and severity of posttraumatic neurobehavioral problems and guide prognostic and therapeutic formulations. The use of standardized assessments also improves the reliability of examinations performed by different CCU staff members, and data derived from these measures can be used to track not only spontaneous recovery but also changes (improvement or decline) in response to treatment.

During the period of posttraumatic coma, the Coma/Near-Coma Scale [131] may be used to gauge coma severity and to monitor recovery. As patients emerge from posttraumatic coma, the assessment of posttraumatic

delirium may be facilitated by the Delirium Rating Scale-Revised-98 [132]; concurrently, serial assessment of PTA using the O-Log [29] should be initiated. After patients emerge from posttraumatic delirium, continued assessment using the O-Log continues until patients meets criteria for emergence from PTA (scores $\geq$25 on 2 consecutive days). During this period, other neuropsychiatric disturbances, such as depression, mania, pathologic laughing and crying, anxiety disorders, psychosis, and nondelirium-related impulse control problems and aggression may develop or be identified more easily as problems not better accounted for by posttraumatic delirium. When there is concern about the development of these problems, neuropsychiatric consultation should be obtained before instituting definitive treatments directed at them. During or shortly after the period of PTA, further evaluation of cognition using the Mini–Mental State Examination [133] and Frontal Assessment Battery [134] may be used to characterize the severity of posttraumatic dysexecutive syndrome [135] and to guide rehabilitative treatment planning.

The neurobehavioral evaluation is complemented usefully by structural neuroimaging. Obtaining neuroimaging using at least CT of the brain is recommended for all patients who have suspected TBI [85]. The authors also recommended MRI when formulating a neurobehavioral treatment plan, on the basis that understanding the anatomy of injury informs on neurobehavioral diagnosis and guides treatment selection usefully. For example, destructive or ablative injury to the lateral orbitofrontal cortices and underlying white matter is a common consequence of severe TBI and is associated with impulsive, disinhibited, or aggressive behavior. Neuroimaging demonstrating severe damage to these areas suggests that pharmacologic agents (eg, selective serotonin reuptake inhibitors [SSRIs], anticonvulsants, or atypical antipsychotics) may be required to suppress brain (limbic) areas driving these behaviors. By contrast, neuroimaging demonstrating injury restricted to cerebral white matter with axonal sparing or revealing no imaging abnormalities suggests a higher likelihood of improving neurobehavioral function through pharmacologic interventions designed to augment the function of the lateral orbitofrontal-subcortical circuit (eg, treatment with psychostimulants or cholinesterase inhibitors). These represent very different approaches to the treatment of posttraumatic impulsive, disinhibited, or aggressive behaviors, and ones that may be informed usefully by neuroimaging rather than empiric treatment trials alone. When MRI is performed, requesting T1, fluid-attenuated inversion recovery, T2* gradient-echo, susceptibility-weighted, and diffusion-weighted sequences is recommended.

Treatment of posttraumatic neurobehavioral disturbances

The selection of treatments for posttraumatic neurobehavioral disturbances is best guided by the published literature specific to TBI. As discussed previously, some agents (eg, haloperidol and benzodiazepines)

used routinely in the management of other critically ill patients may not be well suited for use in this population. Unfortunately, the majority of the treatment literature regarding posttraumatic neurobehavioral disturbances consists of open-label case series, single case reports, and only a few small-scale randomized, double-blind, placebo-controlled studies, leaving unanswered many questions about the safety, tolerability, efficacy, and effectiveness of most agents used in this population. Additionally, no medication has received approval from the United States Food and Drug Administration for the treatment of any neuropsychiatric consequence of TBI. The suggestions offered in this article represent, therefore, a combination of the published literature and the authors' clinical experience and all of them must be regarded as off-label uses. Clinicians are encouraged to consider the application of these agents to the treatment of individual patients a matter of empiric trial.

Posttraumatic coma

If other agents that impair consciousness have been eliminated and posttraumatic coma (including vegetative and minimally conscious states) is the dominant feature of PTE, a combination of environmental, nonpharmacologic, and pharmacologic interventions should be considered. Environmental intervention is recommended for the purpose of facilitating adaptive engagement with staff and relevant portions of the environment while minimizing the potential for overstimulation. For example, providing cues to entrain sleep-wake cycles (lights off and in-room alarms silenced at night, lights on during day) and appetitive or feeding rhythms (bolus rather than continuous feeding) may be useful. Avoiding unnecessary procedures, particularly at odd hours, is suggested and optimizing pain management (analgesia without sedation, where possible) is required. Although the evidence supporting the use of sensory stimulation (''coma stimulation'') treatment protocols is limited [136], the low-cost and minimal risk of these interventions merits consideration of their use for patients in posttraumatic coma in a CCU.

Although opportunities to treat posttraumatic coma directly in the ICU setting occur infrequently, when they do occur, medications that directly or indirectly augment catecholaminergic function are used most often for the treatment of posttraumatic coma and hypoarousal. These agents include amantadine (target dose 50–200 mg twice daily), bromocriptine (1.25–2.5 mg twice daily), carbidopa or levodopa (target dose 25/100 to 25/250 up to 4 times daily), and methylphenidate (target dose 0.3 mg/kg twice daily). Although studies are available to support the use of all of these agents for this purpose, the evidence favors amantadine as the first-line agent for the treatment of posttraumatic coma [137,138]. Treatment generally begins with amantadine (50 mg twice daily), and may be increased weekly (by 100 mg/day) to achieve symptomatic improvement, medication intolerance, or maximum dosage (200 mg twice daily). Monitoring for side effects, in

particular evidence of potentiation of anticholinergic agents and seizures, is required. If amantadine is ineffective or not tolerated, discontinuing it and initiating treatment with bromocriptine may be of benefit; treatment begins with 1.25 mg twice daily and may be advanced after 3 to 7 days to 2.5 mg twice daily. If necessary, additional serial trials of other agents (eg, carbidopa or levodopa and methylphenidate) may be attempted. By the time empiric trials of other agents are undertaken, however, patients usually are in a setting other than a CCU (ie, acute rehabilitation, long-term acute care, or skilled nursing facilities).

Posttraumatic delirium

After patients emerge from posttraumatic coma, a period of posttraumatic delirium generally is expected. The combination of severe alterations or fluctuations of consciousness and impaired selective attention (confusion), restlessness or agitation, aggression, hallucinations, paranoid or other odd ideation, and affective lability presents substantial management challenges for CCU staff. These challenges are compounded when these behaviors lead patients to pull on or pull out intravenous (IV) lines, attempt self-extubation, transfer unsafely, or become threatening or assaultive to family or staff. These behaviors frequently prompt the use of high-dose haloperidol or other D2 receptor antagonists, benzodiazepines, opiates, and other sedating medications. As discussed previously, these treatments pose some theoretic risk for interfering with neuronal recovery and plasticity and their use may delay clinical recovery.

The pathophysiology of delirium—regardless of the context in which it develops—seems to involve an imbalance between cerebral dopaminergic (excessive) and cholinergic (deficient) function [139]. In light of the neurochemical disturbances produced by TBI (discussed previously), the pharmacologic treatment of posttraumatic delirium, therefore, may be undertaken most productively through the use of agents that facilitate cholinergic function or maintain normal dopaminergic function. Although the cholinesterase inhibitors (eg, donepezil, rivastigmine, galantamine, and physostigmine) are, in principle, useful for patients whose delirium-related behavioral disturbances are predicated on cholinergic deficit, the evidence supporting their use for this purpose is limited [140]. Atypical antipsychotics seem as effective as haloperidol for the treatment of delirium in patients who are critically ill (including those who are mechanically ventilated), tend not to interfere strongly with cerebral dopaminergic function, and produce fewer adverse motor effects than haloperidol [141]. These agents also may facilitate, or at least not adversely affect, cognition when used for the treatment of posttraumatic delirium, although there currently are limited data with which to support this suggestion [142,143].

The authors generally use quetiapine as first-line for the treatment of posttraumatic delirium in the CCU among patients in whom enteral

administration is possible. Treatment usually begins with quetiapine (25–50 mg twice daily) and increases rapidly to treatment response or intolerance. In general, most patients seem to respond to quetiapine (600 mg or less total daily dose), although substantially higher doses sometimes are required to achieve reduction of agitiated, aggressive, and other disinhibited behaviors. When enteral administration is not possible, olanzapine may be administered by intramuscular (IM) injection. Treatment usually begins with olanzapine (2.5 mg IM every 12 hours), and may be advanced to olanzapine (5 mg every 6 hours) as tolerated. In general, the total daily dose of olanzapine IM is kept below 20 mg. If these agents are not fully effective in the management of agitation or aggression resulting from posttraumatic delirium, adjunctive or alternative treatment with valproate (starting at 250–500 mg 3 times daily orally or IV) may be helpful.

If all of these interventions fail, then treatment with haloperidol 0.5 to 1 mg twice daily (by mouth, IM, or IV) may be considered. When used, haloperidol doses should not exceed 10 mg daily. At this dose, more than 80% of striatal D2 receptors are occupied and extrapyramidal effects become likely [144]. Further, the apparent effectiveness of high-dose haloperidol likely reflects its additional dose-dependent effects on α-1 adrenergic and serotonin type-2A receptors [145]. If these effects are required to achieve improvement in the symptoms of posttraumatic delirium, then using an atypical antipsychotic as monotherapy, preferably, or as an adjunct to low-dose haloperidol is likely to be as effective as high-dose haloperidol neurobehaviorally and less problematic with respect to extrapyramidal symptoms.

The short-term use of benzodiazpines is appropriate for the treatment of alcohol withdrawal or delirium tremens in patients who have TBI. Their use in the acute period after TBI is otherwise discouraged strongly.

Concurrent to pharmacotherapy, environmental and behavioral interventions of posttraumatic delirium are necessary [146]. Controlling the environment in a manner that decreases the likelihood of sensory overstimulation and subsequent agitation is helpful, even if sometimes difficult to achieve in a CCU. Normalizing light cues to better simulate day-night periods may help entrain sleep-wake cycles. Proactively reorienting patients to current circumstances and surroundings may help avoid frustration and agitation borne of a patient's confusion on these points. Additionally, 1:1 staffing (sitters) in lieu of physical restraints is encouraged, as the latter predictably increase agitation in confused patients, prompting medication administration and sedation that prolong further the period of confusion and agitation.

Posttraumatic amnesia

After emerging from posttraumatic delirium, most patients who have moderate or severe TBI continue to exhibit impairments in declarative

memory (new learning and retrieval) and disturbances in executive function. The memory impairments generally are striking; hence, this period (PTA) is named for them, and they are an appropriate focus of nonpharmacologic and pharmacologic treatment. Among the currently available pharmacotherapies, the cholinesterase inhibitors seem the most useful for the treatment of posttraumatic memory impairments (reviewed by Arciniegas and Silver [61] and Warden and colleagues [82]). Among patients who respond to these agents, attention and executive function often also improve concurrently. Such benefits seem conferred by this entire class of medication, leaving route of administration, dosing, and tolerability as the primary determinants of treatment selection.

Among patients in whom enteral administration is possible, donepezil 5 mg daily generally is used as the first-line treatment. After 2 weeks, the dose may be advanced to donepezil 10 mg daily. When enteral administration is not possible, IV physostigmine (3–12 mg daily, usually in 3 to 4 divided doses) or transdermal rivastigmine (4.6–9.5 mg/24-hour patch) may be considered. The administration frequency and side-effect profile of physostigmine are not favorable, although there are data supporting its use for the treatment of posttraumatic memory impairments in the acute and late post-injury periods. There are no published studies of transdermal rivastigmine among persons who have TBI; it is likely that this agent affords benefits similar to those of the other cholinesterase inhibitors. The safety, tolerability, efficacy, and effectiveness of this agent for PTA, however, remain uncertain and its use, if undertaken at all, requires caution. When used, the rivastigmine patch is initiated at 4.6 mg per 24 hours, and should not be increased to 9.5 mg per 24 hours before the end of 4 weeks of treatment at the starting dose.

Impairments in speed of processing, higher-level (sustained, divided, alternating) attention, working memory, and executive function also generally are present during the period of PTA, although they may be less salient features of the clinical presentation as a result of the striking character of a patient's amnesia. When a cholinesterase inhibitor is used, some of these other cognitive impairments also may improve (in particular attention and executive function). Among patients who have clinically significant impairments in processing speed or impairments in higher-level attention, administration of methylphenidate (5 mg twice daily, titrated in 5-mg twice-daily increments every 2 to 3 days to a target dose of 0.3 mg/kg twice daily) may be of benefit. This treatment may secondarily benefit depressive and affective disturbances and may improve agitation or impulsivity among persons who have intact lateral orbitofrontal-subcortical circuitry (ie, lateral orbitofrontal cortex, subadjacent white matter, and relevant subcortical structures).

Among patients requiring treatment for intermittent agitation or aggression or disinhibition resulting from destructive or ablative lateral orbitofrontal-subcortical system injury, methylphenidate and other catecholamine-augmenting agents should be used with caution if used at all.

In these patients, treatment with valproate or atypical antipsychotics in the manner described for posttraumatic delirium may be useful. When depression, anxiety, or pathologic laughing and crying develop during the period of PTA, treatment with SSRIs may be useful. Among the SSRIs, sertraline, citalopram, and escitalopram are preferred in light of their short half-lives, limited drug-drug interactions, and absence of antimuscarinic effects. When any of these or other neurobehavioral problems develop in the acute postinjury period, consultation with a neuropsychiatrist or behavioral neurologist experienced in their management is encouraged.

Nonpharmacologic interventions also are important during the period of PTA and include errorless learning (the proactive provision of correct information to facilitate learning and avoid intrusions and frustration), cueing and direction for daily tasks, and patient/family/staff training and support. Although none of these interventions seems to hasten the recovery process, their use may decrease frustration and reduce the emergence of unwanted behaviors resulting from memory failures (including confabulation, agitation, and affective lability). During this period of recovery, involving rehabilitation staff (ie, physical therapy, occupational therapy, and speech-language pathology) in the CCU-based management of patients and initiating referral to acute rehabilitation services are appropriate and recommended.

Posttraumatic dysexecutive syndrome

After emerging from PTA, many patients who have moderate or severe TBI continue to demonstrate functionally significant impairments in higher-level attention, processing speed, working memory, memory retrieval (more than new learning), functional communication, and executive function. These impairments frequently are accompanied by other disturbances in emotion (eg, depression, pathologic laughing and crying, and anxiety) and focal neurobehavioral syndromes (eg, disinhibition or aggression resulting from lateral orbitofrontal injury, apathy resulting from bilateral anterior cingulate injury, and partial Klüver-Bucy–like states resulting from bilateral anteromedial temporal injury).

When the occasion for their treatment presents itself in the critical care setting, following the recommendations for treatment of cognitive, emotional, and behavioral sequelae of TBI (discussed previously) is suggested. Consultation and in-CCU management of posttraumatic neurobehavioral disturbances by a physiatrist, rehabilitation staff, and a neuropsychiatrist or behavioral neurologist pending transfer of a patient to an inpatient or outpatient neurorehabilitation program is suggested.

Summary

TBI is a significant public health problem and individuals who have TBI commonly are encountered in critical care settings. The biomechanics of

a typical brain injury result in a predictable injury profile that often involves frontal and temporal cortex, cerebral white matter, diencephalic, and mesencephalic-brainstem areas. Damage to these regions is associated with a constellation of neurobehavioral sequelae, including altered arousal, impaired cognition, agitation, and impairment of impulse control. The response to and recovery from TBI are usefully framed as a PTE with several predictable stages. Patients usually present initially with a disorder of consciousness (coma or hypoarousal). This is followed by a period of altered consciousness, inattention, and behavioral disturbances consistent with a posttraumatic delirium. Over time, the delirium lessens revealing more clearly prominent deficits in new learning and memory (PTA). As memory improves, many patients continued to experience significant impairments in executive function, including impairment in judgment, planning, self-monitoring, and social comportment. The duration of PTA and the degree of recovery from the posttraumatic dysexecutive syndrome are important to assess and monitor as they are highly predictive of eventual functional outcome. Treatment approaches vary across these different stages but there are several broad principles that are important to consider. These include careful attention to other medical conditions (eg, seizures, infections, and pain), reduction or elimination (where possible) of psychotropic medications (eg, benzodiazepines, typical antipsychotics, and anticonvulsants), and management of environmental factors that can cause or exacerbate challenging behaviors or hinder recovery. These considerations may assist critical care practitioners in their efforts to improve not only mortality and medical morbidity but also neurobehavioral outcome after TBI.

References

[1] Thurman D, Guerrero J. Trends in hospitalization associated with traumatic brain injury. JAMA 1999;282(10):954–7.
[2] Thurman DJ, Alverson C, Dunn KA, et al. Traumatic brain injury in the United States: a public health perspective. J Head Trauma Rehabil 1999;14(6):602–15.
[3] Brooks CA, Gabella B, Hoffman R, et al. Traumatic brain injury: designing and implementing a population-based follow-up system. Arch Phys Med Rehabil 1997;78(8 Suppl 4): S26–30.
[4] Levin HS. Neurobehavioral outcome of closed head injury: implications for clinical trials. J Neurotrauma 1995;12(4):601–10.
[5] Levin HS, Gary HE Jr, Eisenberg HM, et al. Neurobehavioral outcome 1 year after severe head injury. Experience of the traumatic coma data bank. J Neurosurg 1990; 73(5):699–709.
[6] Rapoport M, McCauley S, Levin H, et al. The role of injury severity in neurobehavioral outcome 3 months after traumatic brain injury. Neuropsychiatry Neuropsychol Behav Neurol 2002;15(2):123–32.
[7] Marr AL, Coronado VG. Central Nervous System Injury Surveillance Data Submission Standards - 2002. Atlanta, GA, Department of Health and Human Services, Centers for Disease Control and Prevention National Center for Injury Prevention and Control, 2002.
[8] Kaufman HH, Levin HS, High WM Jr, et al. Neurobehavioral outcome after gunshot wounds to the head in adult civilians and children. Neurosurgery 1985;16(6):754–8.

[9] Dikmen S, Machamer J, Miller B, et al. Functional status examination: a new instrument for assessing outcome in traumatic brain injury. J Neurotrauma 2001;18(2):127–40.
[10] Dikmen SS, Machamer JE, Powell JM, et al. Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil 2003;84(10):1449–57.
[11] Hall KM, Bushnik T, Lakisic-Kazazic B, et al. Assessing traumatic brain injury outcome measures for long-term follow-up of community-based individuals. Arch Phys Med Rehabil 2001;82(3):367–74.
[12] Doctor JN, Castro J, Temkin NR, et al. Workers' risk of unemployment after traumatic brain injury: a normed comparison. J Int Neuropsychol Soc 2005;11(6):747–52.
[13] Guilmette TJ, Paglia MF. The public's misconception about traumatic brain injury: a follow up survey. Arch Clin Neuropsychol 2004;19(2):183–9.
[14] Swift TL, Wilson SL. Misconceptions about brain injury among the general public and non-expert health professionals: an exploratory study. Brain Inj 2001;15(2):149–65.
[15] Marr AL, Coronado VG. Central nervous system injury surveillance data submission standards—2002. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention National Center for Injury Prevention and Control; 2002.
[16] Kraus JF, Rice TM, Peek-Asa C, et al. Facial trauma and the risk of intracranial injury in motorcycle riders. Ann Emerg Med 2003;41(1):18–26.
[17] Johnston JJ. The galasko report implemented: the role of emergency medicine in the management of head injuries. Eur J Emerg Med 2007;14(3):130–3.
[18] Palchak MJ, Holmes JF, Vance CW, et al. A decision rule for identifying children at low risk for brain injuries after blunt head trauma. Ann Emerg Med 2003;42(4):492–506.
[19] Borg J, Holm L, Cassidy JD, et al. Diagnostic procedures in mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med 2004 February;36(Suppl 43):61–75.
[20] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81–4.
[21] Gabbe BJ, Cameron PA, Finch CF. The status of the Glasgow coma scale. Emerg Med (Fremantle) 2003;15(4):353–60.
[22] Clifton GL, Hayes RL, Levin HS, et al. Outcome measures for clinical trials involving traumatically brain-injured patients: report of a conference. Neurosurgery 1992;31(5):975–8.
[23] Cowen TD, Meythaler JM, Devivo MJ, et al. Influence of early variables in traumatic brain injury on functional independence measure scores and rehabilitation length of stay and charges. Arch Phys Med Rehabil 1995;76(9):797–803.
[24] Williams DH, Levin HS, Eisenberg HM. Mild head injury classification. Neurosurgery 1990;27(3):422–8.
[25] van der Naalt J, Hew JM, van Zomeren AH, et al. Computed tomography and magnetic resonance imaging in mild to moderate head injury: early and late imaging related to outcome. Ann Neurol 1999;46(1):70–8.
[26] Levin HS, O'Donnell VM, Grossman RG. The galveston orientation and amnesia test. A practical scale to assess cognition after head injury. J Nerv Ment Dis 1979;167(11):675–84.
[27] Marrosszeky N, Ryan L, Shores EA, et al. The PTA protocol. Guidelines for using the westmead post-traumatic amnesia (PTA) scale. Sydney (Australia): Wild & Wooley; 1998, Ref Type: Pamphlet.
[28] Tate RL, Perdices M, Pfaff A, et al. Predicting duration of posttraumatic amnesia (PTA) from early PTA measurements. J Head Trauma Rehabil 2001;16(6):525–42.
[29] Jackson WT, Novack TA, Dowler RN. Effective serial measurement of cognitive orientation in rehabilitation: the orientation log. Arch Phys Med Rehabil 1998;79(6):718–20.
[30] Novack TA, Dowler RN, Bush BA, et al. Validity of the orientation log, relative to the galveston orientation and amnesia test. J Head Trauma Rehabil 2000;15(3):957–61.
[31] Frey KL, Rojas DC, Anderson CA, et al. Comparison of the O-Log and GOAT as measures of posttraumatic amnesia. Brain Inj 2007;21(5):513–20.

[32] Kay T, Harrington DE, Adams RE, et al. Definition of mild traumatic brain injury: report from the mild traumatic brain injury committee of the head injury interdisciplinary special interest group of the American congress of rehabilitation medicine. J Head Trauma Rehabil 1993;8(3):86–7.
[33] Russell WR, Smith A. Post-traumatic amnesia in closed head injury. Arch Neurol 1961;5: 4–17.
[34] Zafonte RD, Mann NR, Millis SR, et al. Posttraumatic amnesia: its relation to functional outcome. Arch Phys Med Rehabil 1997;78(10):1103–6.
[35] Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975; 1(7905):480–4.
[36] Katz DI, Alexander MP. Traumatic brain injury. Predicting course of recovery and outcome for patients admitted to rehabilitation. Arch Neurol 1994;51(7):661–70.
[37] Ellenberg JH, Levin HS, Saydjari C. Posttraumatic amnesia as a predictor of outcome after severe closed head injury. Prospective assessment. Arch Neurol 1996;53(8): 782–91.
[38] Brooks DN, Aughton ME, Bond MR, et al. Cognitive sequelae in relationship to early indices of severity of brain damage after severe blunt head injury. J Neurol Neurosurg Psychiatry 1980;43(6):529–34.
[39] Geffen GM, Encel JS, Forrester GM. Stages of recovery during post-traumatic amnesia and subsequent everyday memory deficits. Neuroreport 1991;2(2):105–8.
[40] Haslam C, Batchelor J, Fearnside MR, et al. Post-coma disturbance and post-traumatic amnesia as nonlinear predictors of cognitive outcome following severe closed head injury: findings from the westmead head injury project. Brain Inj 1994;8(6):519–28.
[41] Sherer M, Sander AM, Nick TG, et al. Early cognitive status and productivity outcome after traumatic brain injury: findings from the TBI model systems. Arch Phys Med Rehabil 2002;83(2):183–92.
[42] Avesani R, Salvi L, Rigoli G, et al. Reintegration after severe brain injury: a retrospective study. Brain Inj 2005;19(11):933–9.
[43] Doig E, Fleming J, Tooth L. Patterns of community integration 2–5 years post-discharge from brain injury rehabilitation. Brain Inj 2001;15(9):747–62.
[44] Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 2007;21(5):515–31.
[45] Halliday AL. Pathophysiology. In: Marion DW, editor. Traumatic brain injury. New York: Thieme Medical Publishers, Inc.; 1999. p. 29–38.
[46] Cassidy JW. Neuropathology. In: Silver JM, Yudofsky SC, Hales RE, editors. Neuropsychiatry of traumatic brain injury. Washington, DC: American Psychiatric Press, Inc.; 1994. p. 43–79.
[47] Levin HS, Mendelsohn D, Lilly MA, et al. Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the ommaya-gennarelli model. Neurosurgery 1997;40(3):432–40.
[48] Strich SJ. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J Neurol Neurosurg Psychiatry 1956;19(3):163–85.
[49] Sabet AA, Christoforou E, Zatlin B, et al. Deformation of the human brain induced by mild angular head acceleration. J Biomech 2008;41(2):307–15.
[50] Besenski N. Traumatic injuries: imaging of head injuries. Eur Radiol 2002;12(6):1237–52.
[51] Ryan GA, McLean AJ, Vilenius AT, et al. Brain injury patterns in fatally injured pedestrians. J Trauma 1994;36(4):469–76.
[52] Misra JC, Chakravarty S. A study of rotational brain injury. J Biomech 1984;17(7):459–66.
[53] Fijalkowski RJ, Stemper BD, Pintar FA, et al. Biomechanical correlates of mild diffuse brain injury in the rat. Biomed Sci Instrum 2007;43:18–23.
[54] Fijalkowski RJ, Ellingson BM, Stemper BD, et al. Interface parameters of impact-induced mild traumatic brain injury. Biomed Sci Instrum 2006;42:108–13.

[55] Margulies SS, Thibault LE, Gennarelli TA. Physical model simulations of brain injury in the primate. J Biomech 1990;23(8):823–36.
[56] Meythaler JM, Peduzzi JD, Eleftheriou E, et al. Current concepts: diffuse axonal injury-associated traumatic brain injury. Arch Phys Med Rehabil 2001;82(10):1461–71.
[57] Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. J Head Trauma Rehabil 2005;20(1):76–94.
[58] Kraus MF, Susmaras T, Caughlin BP, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 2007;130(Pt 10): 2508–19.
[59] Black KL, Hanks RA, Wood DL, et al. Blunt versus penetrating violent traumatic brain injury: frequency and factors associated with secondary conditions and complications. J Head Trauma Rehabil 2002;17(6):489–96.
[60] Bigler ED. Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. Arch Clin Neuropsychol 2003;18(6):595–621.
[61] Arciniegas DB, Silver JM. Pharmacotherapy of posttraumatic cognitive impairments. Behav Neurol 2006;17(1):25–42.
[62] Alessandri B, Doppenberg E, Bullock R, et al. Glucose and lactate metabolism after severe human head injury: influence of excitatory neurotransmitters and injury type. Acta Neurochir Suppl 1999;75:21–4.
[63] Alessandri B, Reinert M, Young HF, et al. Low extracellular (ECF) glucose affects the neurochemical profile in severe head-injured patients. Acta Neurochir Suppl 2000;76: 425–30.
[64] Phillips LL, Reeves TM. Interactive pathology following traumatic brain injury modifies hippocampal plasticity. Restor Neurol Neurosci 2001;19(3–4):213–35.
[65] Pappius HM. Involvement of indoleamines in functional disturbances after brain injury. Prog Neuropsychopharmacol Biol Psychiatry 1989;13(3–4):353–61.
[66] Tsuiki K, Takada A, Nagahiro S, et al. Synthesis of serotonin in traumatized rat brain. J Neurochem 1995;64(3):1319–25.
[67] Meythaler JM, Depalma L, Devivo MJ, et al. Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. Brain Inj 2001;15(4): 321–31.
[68] Wilson MS, Hamm RJ. Effects of fluoxetine on the 5-HT1A receptor and recovery of cognitive function after traumatic brain injury in rats. Am J Phys Med Rehabil 2002;81(5): 364–72.
[69] Goldstein LB. Neurotransmitters and motor activity: effects on functional recovery after brain injury. NeuroRx 2006;3(4):451–7.
[70] Goldstein LB. Neuropharmacology of TBI-induced plasticity. Brain Inj 2003;17(8):685–94.
[71] Goldstein LB. Effects of amphetamines and small related molecules on recovery after stroke in animals and man. Neuropharmacology 2000;39(5):852–9.
[72] Rao N, Jellinek HM, Woolston DC. Agitation in closed head injury: haloperidol effects on rehabilitation outcome. Arch Phys Med Rehabil 1985;66(1):30–4.
[73] Markianos M, Seretis A, Kotsou A, et al. CSF neurotransmitter metabolites in comatose head injury patients during changes in their clinical state. Acta Neurochir (Wien) 1996; 138(1):57–9.
[74] Markianos M, Seretis A, Kotsou S, et al. CSF neurotransmitter metabolites and short-term outcome of patients in coma after head injury. Acta Neurol Scand 1992;86(2):190–3.
[75] Salmond CH, Chatfield DA, Menon DK, et al. Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain 2005;128(Pt 1):189–200.
[76] Murdoch I, Nicoll JA, Graham DI, et al. Nucleus basalis of meynert pathology in the human brain after fatal head injury. J Neurotrauma 2002;19(2):279–84.
[77] Dewar D, Graham DI. Depletion of choline acetyltransferase activity but preservation of M1 and M2 muscarinic receptor binding sites in temporal cortex following head injury: a preliminary human postmortem study. J Neurotrauma 1996;13(4):181–7.

[78] Murdoch I, Perry EK, Court JA, et al. Cortical cholinergic dysfunction after human head injury. J Neurotrauma 1998;15(5):295–305.
[79] McAllister TW, Flashman LA, Sparling MB, et al. Working memory deficits after traumatic brain injury: catecholaminergic mechanisms and prospects for treatment—a review. Brain Inj 2004;18(4):331–50.
[80] Lipsky RH, Sparling MB, Ryan LN, et al. Role of COMT val108/158 met genotype in executive functioning following TBI. J Neuropsychiatry Clin Neurosci 2002;14(1):116.
[81] Arciniegas DB. The cholinergic hypothesis of cognitive impairment caused by traumatic brain injury. Curr Psychiatry Rep 2003;5(5):391–9.
[82] Warden DL, Gordon B, McAllister TW, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma 2006;23(10): 1468–501.
[83] Bogdanovitch UJ, Bazarevitch GJ, Kirillov AL. The use of cholinesterase in severe head injury. Resuscitation 1975;4(2):139–41.
[84] Calatayud M, Calatayud V, Aso EJ. Effects of CDP-choline on the recovery of patients with head injury. J Neurol Sci 1991;103(Suppl):S15–8.
[85] Marion DW. Evidenced-based guidelines for traumatic brain injuries. Prog Neurol Surg 2006;19:171–96.
[86] Lew HL. Rehabilitation needs of an increasing population of patients: traumatic brain injury, polytrauma, and blast-related injuries. J Rehabil Res Dev 2005;42(4):xiii–xxvi.
[87] Sayer NA, Chiros CE, Sigford B, et al. Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the global war on terror. Arch Phys Med Rehabil 2008;89(1):163–70.
[88] Trudeau DL, Anderson J, Hansen LM, et al. Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion. J Neuropsychiatry Clin Neurosci 1998;10(3):308–13.
[89] Bochicchio GV, Lumpkins K, O'Connor J, et al. Blast injury in a civilian trauma setting is associated with a delay in diagnosis of traumatic brain injury. Am Surg 2008;74(3): 267–70.
[90] Kluger Y, Nimrod A, Biderman P, et al. The quinary pattern of blast injury. Am J Disaster Med 2007;2(1):21–5.
[91] Warden D. Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil 2006;21(5):398–402.
[92] Guy RJ, Glover MA, Cripps NP. Primary blast injury: pathophysiology and implications for treatment. Part III: Injury to the central nervous system and the limbs. J R Nav Med Serv 2000;86(1):27–31.
[93] Mayorga MA. The pathology of primary blast overpressure injury. Toxicology 1997; 121(1):17–28.
[94] Gruss E. A correction for primary blast injury criteria. J Trauma 2006;60(6):1284–9.
[95] Born CT. Blast trauma: the fourth weapon of mass destruction. Scand J Surg 2005;94(4): 279–85.
[96] Phillips YY. Primary blast injuries. Ann Emerg Med 1986;15(12):1446–50.
[97] Cernak I, Wang Z, Jiang J, et al. Cognitive deficits following blast injury-induced neurotrauma: possible involvement of nitric oxide. Brain Inj 2001;15(7):593–612.
[98] Cernak I, Wang Z, Jiang J, et al. Ultrastructural and functional characteristics of blast injury-induced neurotrauma. J Trauma 2001;50(4):695–706.
[99] Cernak I, Savic J, Malicevic Z, et al. Involvement of the central nervous system in the general response to pulmonary blast injury. J Trauma 1996;40(Suppl 3):S100–4.
[100] Zunic G, Romic P, Vueljic M, et al. Very early increase in nitric oxide formation and oxidative cell damage associated with the reduction of tissue oxygenation is a trait of blast casualties. Vojnosanit Pregl 2005;62(4):273–80.
[101] Moochhala SM, Md S, Lu J, et al. Neuroprotective role of aminoguanidine in behavioral changes after blast injury. J Trauma 2004;56(2):393–403.

[102] Kaur C, Singh J, Lim MK, et al. The response of neurons and microglia to blast injury in the rat brain. Neuropathol Appl Neurobiol 1995;21(5):369–77.
[103] Irwin RJ, Lerner MR, Bealer JF, et al. Shock after blast wave injury is caused by a vagally mediated reflex. J Trauma 1999;47(1):105–10.
[104] Irwin RJ, Lerner MR, Bealer JF, et al. Global primary blast injury: a rat model. J Okla State Med Assoc 1998;91(7):387–92.
[105] Guy RJ, Kirkman E, Watkins PE, et al. Physiologic responses to primary blast. J Trauma 1998;45(6):983–7.
[106] Anderson CV, Wood DM, Bigler ED, et al. Lesion volume, injury severity, and thalamic integrity following head injury. J Neurotrauma 1996;13(2):59–65.
[107] Wood DM, Bigler ED. Diencephalic changes in traumatic brain injury: relationship to sensory perceptual function. Brain Res Bull 1995;38(6):545–9.
[108] Rothman MS, Arciniegas DB, Filley CM, et al. The neuroendocrine effects of traumatic brain injury. J Neuropsychiatry Clin Neurosci 2007;19(4):363–72.
[109] Hagen C, Malkmus D, Durham P. Rancho Los Amigos Scale. Communication Disorders Service, Rancho Los Amigos Hospital; 1972.
[110] Gouvier WD, Blanton PD, LaPorte KK, et al. Reliability and validity of the disability rating scale and the levels of cognitive functioning scale in monitoring recovery from severe head injury. Arch Phys Med Rehabil 1987;68(2):94–7.
[111] Vespa P. Continuous EEG monitoring for the detection of seizures in traumatic brain injury, infarction, and intracerebral hemorrhage: ''to detect and protect''. J Clin Neurophysiol 2005;22(2):99–106.
[112] Vespa PM, Nenov V, Nuwer MR. Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. J Clin Neurophysiol 1999;16(1):1–13.
[113] Kolakowsky-Hayner SA, Gourley EV 3rd, Kreutzer JS, et al. Pre-injury substance abuse among persons with brain injury and persons with spinal cord injury. Brain Inj 1999; 13(8):571–81.
[114] Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 2003; 44(Suppl 10):11–7.
[115] Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev 2000;(2):CD000173.
[116] Dikmen SS, Temkin NR, Miller B, et al. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA 1991;265(10):1271–7.
[117] Smith KR Jr, Goulding PM, Wilderman D, et al. Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: a comparative study. Arch Neurol 1994;51(7):653–60.
[118] Szaflarski JP, Meckler JM, Szaflarski M, et al. Levetiracetam use in critically ill patients. Neurocrit Care 2007;7(2):140–7.
[119] Ruegg S, Naegelin Y, Hardmeier M, et al. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav 2008;12(3):477–80.
[120] Mula M, Trimble MR, Sander JW. Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam. Seizure 2004;13(1):55–7.
[121] Mula M, Trimble MR, Yuen A, et al. Psychiatric adverse events during levetiracetam therapy. Neurology 2003;61(5):704–6.
[122] Dikmen SS, Machamer JE, Winn HR, et al. Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. Neurology 2000;54(4):895–902.
[123] Wong C, Burry L, Molino-Carmona S, et al. Analgesic and sedative pharmacology in the intensive care unit. Dynamics 2004;15(1):23–6.
[124] Milbrandt EB, Kersten A, Kong L, et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 2005;33(1): 226–9.
[125] Goldstein LB. Pharmacological approach to functional reorganization: the role of norepinephrine. Rev Neurol (Paris) 1999;155(9):731–6.

[126] Goldstein LB. Basic and clinical studies of pharmacologic effects on recovery from brain injury. J Neural Transplant Plast 1993;4(3):175–92.
[127] Stanislav SW. Cognitive effects of antipsychotic agents in persons with traumatic brain injury. Brain Inj 1997;11(5):335–41.
[128] Buffett-Jerrott SE, Stewart SH. Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des 2002;8(1):45–58.
[129] Bleiberg J, Garmoe W, Cederquist J, et al. Effects of dexedrine on perfomance consistency following brain injury: a double-blind placebo crossover case study. Neuropsychiatry Neuropsychol Behav Neurol 1993;6(4):245–8.
[130] McCarter RJ, Walton NH, Moore C, et al. PTA testing, the westmead post traumatic amnesia scale and opiate analgesia: a cautionary note. Brain Inj 2007;21(13–14):1393–7.
[131] Rappaport M. The disability rating and coma/near-coma scales in evaluating severe head injury. Neuropsychol Rehabil 2005;15(3–4):442–53.
[132] Trzepacz PT, Mittal D, Torres R, et al. Validation of the delirium rating scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001;13(2):229–42.
[133] Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[134] Dubois B, Slachevsky A, Litvan I, et al. The FAB: a frontal assessment battery at bedside. Neurology 2000;55:1621–6.
[135] Arciniegas DB, Frey K, Alderfer B, et al. Impairments of frontally-mediated cognition characterize posttraumatic encephalopathy following resolution of posttraumatic amnesia. J Neuropsychiatry Clin Neurosci 2006;18(2):281.
[136] Lombardi F, Taricco M, De TA, et al. Sensory stimulation for brain injured individuals in coma or vegetative state. Cochrane Database Syst Rev 2002;(2):CD001427.
[137] Meythaler JM, Brunner RC, Johnson A, et al. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. J Head Trauma Rehabil 2002;17(4):300–13.
[138] Whyte J, Katz D, Long D, et al. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: a multicenter study. Arch Phys Med Rehabil 2005;86(3):453–62.
[139] Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000;5(2):132–48.
[140] Overshott R, Karim S, Burns A. Cholinesterase inhibitors for delirium. Cochrane Database Syst Rev 2008;(1):CD005317.
[141] Rea RS, Battistone S, Fong JJ, et al. Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. Pharmacotherapy 2007;27(4):588–94.
[142] Oster TJ, Anderson CA, Filley CM, et al. Quetiapine for mania due to traumatic brain injury. CNS Spectr 2007;12(10):764–9.
[143] Kim E, Bijlani M. A pilot study of quetiapine treatment of aggression due to traumatic brain injury. J Neuropsychiatry Clin Neurosci 2006;18(4):547–9.
[144] Kapur S, Zipursky R, Roy P, et al. The relationship between D2 receptor occupancy and plasma levels on low dose oral haloperidol: a PET study. Psychopharmacology (Berl) 1997;131(2):148–52.
[145] Schotte A, Janssen PF, Megens AA, et al. Occupancy of central neurotransmitter receptors by risperidone, clozapine and haloperidol, measured ex vivo by quantitative autoradiography. Brain Res 1993;631(2):191–202.
[146] Trzepacz PT, Kennedy RE. Delirium and posttraumatic amnesia. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. p. 175–200.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 767–788

CRITICAL
CARE
CLINICS

Substance Abuse and Withdrawal in the Critical Care Setting

Jeanette M. Tetrault, MD*,
Patrick G. O'Connor, MD, MPH

Section of General Internal Medicine, Yale University School of Medicine, Yale-New Haven Hospital, 333 Cedar Street, New Haven, CT 06520–8025, USA

Approximately 30% of Americans currently use tobacco products, 51% currently use alcohol, and 8% currently use illicit drugs [1]. Substance use has been shown to cause significant morbidity and mortality. The first and third leading causes of death in the United States are tobacco use (18.1% of all deaths) and alcohol consumption (3.5% of all deaths) [2]. Substance use often underlies hospital admissions for accidents and injury and presents a major financial burden to the United States health care system [3,4]. Globally, the burden of alcohol, tobacco, and illicit drug use has enormous impact on international public health on both the epidemiologic and economic scales [5].

Substance abuse is considered a maladaptive pattern of substance use resulting in repeated adverse social consequences; substance dependence, the most severe form of abuse, is characterized by physiologic and behavioral symptoms related to substance use (Table 1). Approximately 9% of the United States population (22.6 million persons), 12 years of age or older, meet criteria established by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* for substance abuse or dependence [1]. Specifically, 7% of the population meets criteria for alcohol abuse or dependence, whereas 3% meets criteria for illicit substance abuse or dependence. The illicit substances most commonly used include marijuana, cocaine, and prescription opioids [1].

Drs. Tetrault and O'Connor were funded through the Department of Internal Medicine, Yale University School of Medicine, during the preparation of this publication.

* Corresponding author.
E-mail address: jeanette.tetrault@yale.edu (J.M. Tetrault).

doi:10.1016/j.ccc.2008.05.005

Table 1
Diagnostic and Statistical Manual-IV criteria for substance abuse and withdrawal[a]

Abuse	Dependence
Defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period:	Defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:
1. Recurrent use resulting in failure to fulfill major role obligation at work, home, or school	1. Tolerance, characterized by either:
2. Recurrent use in physically hazardous situations	(a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect or
3. Recurrent substance-related legal problems	(b) Markedly diminished effect with continued use of the same amount of the substance
4. Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	2. Withdrawal, characterized by either:
	(a) The characteristic withdrawal syndrome for the substance or
	(b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
	3. Substance taken in larger amount and for longer period than intended
	4. Persistent desire or repeated unsuccessful attempt to quit
	5. Much time or activity to obtain, use, recover from effects of substance
	6. Important social, occupational, or recreational activities given up or reduced
	7. Use continues despite knowledge of adverse consequences

[a] According to the *Diagnostic and Statistical Manual of Mental Disorders*. 4th edition, a person can be abusing a substance or dependent on a substance but not both at the same time.

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington DC: American Psychiatric Association; 1994.

Substance use among trauma and critically ill patients

Substance use is often associated with motor vehicle accidents, falls, drownings, thermal injury, homicide, and suicide [3,6–8]. Many studies have noted a significant association between alcohol use and injury [3,7–10]. One review of articles published between 1995 and 2005 found that patients presenting to the emergency department were more likely to have a positive blood alcohol concentration and report drinking before the injury than patients presenting for reasons other than injury [7]. In the United States, up to half of trauma beds are occupied by patients involved in alcohol-related traffic accidents [3]. Additionally, cocaine and cannabis use place patients at higher risk for all types of injuries [11].

Alcohol abuse and dependence are found in 10% to 40% of patients admitted to the ICU and are associated with doubling of mortality [12]. Alcohol use can lead to multiple metabolic and systemic derangements including thiamine deficiency and subsequent Wernicke's encephalopathy, hypomagnesemia, hypokalemia, hypophosphatemia, metabolic acidosis, rhabdomyolysis, hepatic insufficiency, and pancreatitis [12]. Chronic alcohol use has been independently associated with acute respiratory distress syndrome (odds ratio, 3.70; 95% confidence interval, 1.83–7.71) and increases the severity of multiorgan dysfunction in patients with underlying septic shock [13,14].

Common withdrawal-related issues

Withdrawal syndromes are physiologic responses to abrupt withdrawal or reduced use of a drug and are common to many substances of abuse. These syndromes may often complicate the care of critically ill patients [6,15,16]. It may be especially challenging to treat patients with substance withdrawal syndromes because of an unknown history of substance abuse, altered mental status, or complex physiologic responses resulting from the presenting illness, which can be confused with withdrawal [17]. Withdrawal syndromes have been associated with the use of alcohol [18], opioids [19], cocaine [20], benzodiazepines [21], marijuana [22], and nicotine [23]. It is important to screen all high-risk critical care patients by performing urine toxicology for drugs of abuse at the time of admission to the hospital or to a critical care setting.

The management of patients with a substance withdrawal syndrome presenting concomitantly with an underlying critical illness can be especially challenging [24]. The first step in caring for any critically ill patient is to ensure adequate airway management, intravenous access, and application of general resuscitative measures [6]. General principles regarding the management of substance withdrawal syndromes include use of a symptom-triggered approach, substitution of a long-acting replacement for the abused drug in gradual tapering doses, and establishing a plan for long-term abstinence [25]. When assessing for superimposed substance withdrawal, the critical care team must consider potential polysubstance abuse. A thorough substance abuse history should be obtained from the patient or family. It is important to determine which substances a patient may be withdrawing from by taking a thorough substance abuse history and performing urine toxicology on all patients. Common symptoms that underlie many withdrawal syndromes include irritability, dysphoria, anxiety, nausea, agitation, tachycardia, and hypertension [25]. Treatment protocols may vary, however, and treatment of one syndrome may mask symptoms of an additional syndrome, which, if untreated, may be life threatening [25].

Specific withdrawal syndromes

Alcohol withdrawal

Clinical manifestations of alcohol withdrawal

The spectrum of alcohol withdrawal ranges from a mild physiologic response to seizures and death. More severe responses are seen in patients with prior episodes of withdrawal, a phenomenon known as "kindling" [26], or other underlying acute conditions. Chronic alcohol use has a depressant effect on γ-aminobutyric acid transmission with compensatory increased *N*-methyl-D-aspartate and adrenergic activity [25,27]. This sudden increase in adrenergic activity, manifested by increased catecholamine release, is what causes the most common symptoms including tachycardia, hypertension, and tremor [6]. It is important to note that the symptoms of alcohol withdrawal may occur not only with abrupt cessation of alcohol use but also with a reduction in use.

Symptoms of alcohol withdrawal may begin as soon as 6 to 8 hours after decreasing alcohol intake (Table 2). Early symptoms include tremulousness, anxiety, palpitations, nausea, and anorexia [28]. These symptoms typically subside after 24 to 48 hours. Alcohol withdrawal seizures are common in patients with chronic alcohol use and usually occur between 6 and 48 hours after decreasing alcohol use [29–31]. Early recognition and treatment of alcohol-related seizures are important to prevent development of status epilepticus. Approximately 12 to 48 hours after cessation of alcohol use, alcoholic hallucinosis may occur. Alcoholic hallucinosis is characterized by visual, auditory, or tactile hallucinations and is hallmarked by an intact sensorium, in contrast to delirium tremens (DTs) [32,33].

Table 2
Clinical manifestations of alcohol withdrawal

Phase	Symptoms	Onset after last drink	Duration
Early withdrawal	Tremulousness Anxiety Palpitations Nausea Anorexia	6–8 h	1–2 d
Withdrawal seizures	Generalized tonic-clonic seizures	6–48 h	2–3 d
Alcoholic hallucinosis	Hallucinations Visual Tactile Auditory	12–48 h	1–2 d
Delirium tremens	Tachycardia Hypertension Low-grade fever Diaphoresis Delirium Agitation	48–96 h	1–5 d

DTs typically occur 48 to 96 hours after withdrawal of alcohol and are characterized by tachycardia, hypertension, low-grade fever, diaphoresis, and delirium. Approximately 5% of patients experiencing alcohol withdrawal develop DTs. Risk factors for the development of DTs include a prolonged drinking history, previous episodes of DTs, age greater than 30 years, comorbid illness, and a greater number of days since last drink [34]. The syndrome is associated with a 5% to 15% mortality rate and death is often caused by arrhythmias or associated critical illness (eg, pneumonia). Older age, underlying lung disease, fever greater than 104°F, and comorbid liver disease are associated with an increase in mortality risk [34]. Patients with DTs exhibit increased oxygen consumption, respiratory alkalosis caused by hyperventilation, and subsequent decreased cerebral blood flow [35]. As a result of associated hyperthermia, diaphoresis, tachypnea, and vomiting, DTs also often lead to dehydration. Hypokalemia is a common manifestation resulting from both renal and extrarenal losses; hypomagnesemia is also common and may predispose patients to the development of seizures and arrythmias; hypophosphatemia may also be present and contribute to further complications [15,36].

Common complications of chronic alcoholism and alcohol withdrawal need to be considered when caring for a critically ill patient with a history of alcohol abuse. The astute physician should be aware of the classic triad of encephalopathy, oculomotor dysfunction, and gait ataxia associated with Wernicke's encephalopathy, caused by thiamine deficiency [37]. The pathophysiology of this syndrome is poorly understood. Brain lesions are associated with the syndrome and are characterized by vascular congestion, microglial proliferation, and petechial hemorrhages in a symmetric distribution around the third and fourth ventricles. In the chronic state, demyelination may occur. Atrophy of the mamillary bodies is highly specific for this process. The treatment of Wernicke's encephalopathy consists of 100 mg of thiamine intravenously or intramuscularly daily for 5 days, and prognosis depends on prompt administration of thiamine. Care needs to be taken when considering this syndrome because administration of glucose before thiamine replacement may worsen the symptoms. Korsakoff's amnestic syndrome, a late manifestation of Wernicke's encephalopathy, is characterized by selective anterograde and retrograde amnesia [37]. The development of Wernicke-Korsakoff syndrome is best prevented by chronic oral administration of thiamine to outpatients at risk.

Other common complications of chronic alcoholism and alcohol withdrawal include pneumonia, acute respiratory distress syndrome, sepsis, upper gastrointestinal bleeding, necrotizing pancreatitis, and acute and chronic liver disease [38].

Management of alcohol withdrawal

Multiple studies have shown benzodiazepines, particularly ones with longer duration of action, to be the preferred therapy for the treatment of

alcohol withdrawal [25,39–41]. In a randomized trial of 537 patients with alcohol withdrawal, published in 1968, treatment with chlordiazepoxide resulted in a 2% combined risk of seizures and delirium compared with a 10% to 16% risk in patients receiving chlorpromazine, thiamine, hydroxyzine, or placebo [42]. A more recent meta-analysis of 11 studies comparing benzodiazepines with placebo or active control showed that early recognition and treatment of alcohol withdrawal with benzodiazepines reduces duration and severity of symptoms, the incidence of delirium, and seizures [39].

No one benzodiazepine has been proved to be superior for the treatment of alcohol withdrawal [43]. Evidence points to longer-acting benzodiazepines (chlordiazepoxide or valium) to be more effective for the prevention of seizures and DTs, whereas shorter-acting agents (alprazolam or oxazepam) may be associated with the development of seizures during withdrawal.

The dose and duration of benzodiazepine treatment has been a subject of much investigation. A landmark randomized clinical trial from 1994 [44] that compared fixed-dosing of chlordiazepoxide (four times daily) with symptom-triggered dosing found that the fixed-dosing approach required a longer duration of treatment (68 versus 9 hours, $P < .001$) and more medication (425 versus 100 mg of chlordiazepoxide, $P < .001$). No differences were seen in severity of withdrawal or incidence of seizures [44]. Similar results were noted in another study that compared symptom-triggered approach with the treatment of alcohol withdrawal in the ICU with continuous midazolam drip. In this study, use of the symptom-triggered approach was associated with decreased time to symptom control and less benzodiazepine used [45]. The most widely used and validated tool to assess severity of symptoms of alcohol withdrawal is the Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar) (Appendix 1) [46,47]. This tool should be used only after the diagnosis of alcohol withdrawal is made and is useful to guide treatment using the symptom-triggered approach.

Maldonado and colleagues [48] conducted a prospective, randomized study comparing the effects of lorazepam (short half-life) with those of diazepam (long half-life) on physiologic (eg, vital signs) and psychophysiologic responses (eg, CIWA-Ar) of subjects undergoing alcohol withdrawal. The study included 48 inpatients presenting with alcohol withdrawal symptoms at a university and a Veterans Affairs hospitals. They found that there was no significant difference between the rates of change for either group on either measure ($P > .05$). Similarly, there was no significant difference in the total equipotent benzodiazepine usage between groups ($P > .05$). Despite the controversy regarding the benefits of one benzodiazepine agent versus another, this study found no evidence of a clinical advantage for choosing benzodiazepines according to their half-lives. These findings suggest that the choice of benzodiazepine in the management of alcohol withdrawal is not as critical as had been anecdotally assumed.

A recently published study also shows that a significant proportion of patients are inappropriately treated with symptom-triggered therapy for

alcohol withdrawal in hospitalized patients. The authors conclude that more stringent evaluation for this treatment modality is needed [49].

Other medications have been evaluated for the treatment of alcohol withdrawal. β-Blockers have been shown to be effective for symptomatic treatment through reductions in autonomic activity [50]. β-Blockers, however, should not be used as monotherapy and caution should be taken with use of these agents because they may mask signs and symptoms of a worsening clinical scenario. α-Adrenergic agonists, also through reductions in autonomic activity, have also been used in the treatment of alcohol withdrawal. These agents also have no activity against delirium or seizures so should not be used as monotherapy. Carbamazepine has been shown to be superior to placebo for the treatment of alcohol withdrawal and to reduce "kindling" effects [51]. Neuroleptic agents, such as haloperidol, are useful as adjunctive treatment and reduce agitation and hallucinations [52]. Treatment of alcohol withdrawal with a tapering ethyl alcohol infusion offers biologic plausibility. A recent randomized clinical trial in ICU patients, however, found no benefit of treatment with alcohol over diazepam [40].

There is some evidence to suggest that the new α_2-agonist, dexmedetomidine, and other similar agents, may be effective for the treatment of opioid withdrawal. Riihioja and colleagues [53] compared the effects of dexmedetomidine, a selective α_2-adrenoceptor agonist, with those of diazepam and propranolol on alcohol withdrawal symptoms in rats. After the intoxication period (4 days), rats were divided into four equal groups: (1) a dexmedetomidine-treated group (30 μg/kg, subcutaneously); (2) a diazepam-treated group (2 mg/kg, subcutaneously); (3) a propranolol-treated group (5 mg/kg, subcutaneously); and (4) a control group with no medication. Medication was given in the withdrawal phase (2, 8, 14, and 20 hours after the onset of the withdrawal symptoms). The severity of the alcohol withdrawal symptoms (eg, rigidity, tremor, irritability, and hypoactivity) was observed up to 33 hours after the onset of the ethanol withdrawal symptoms. When measured as the sum score of the three most specific withdrawal signs (eg, rigidity, tremor, and irritability), dexmedetornidine and diazepam significantly relieved the ethanol withdrawal reaction, whereas propranolol attenuated tremor, but was inefficient against other withdrawal symptoms. In addition, dexmedetomidine was found to relieve ethanol-induced neuronal loss in the locus ceruleus. Even though there are no human studies, data from case reports suggest that dexmedetomidine may be a valuable adjunct in the treatment of severe cases of alcohol withdrawal by better controlling sympathetic overactivity while providing adequate sedation with minimal respiratory depression [54–56].

Opioid withdrawal

Clinical manifestations of opioid withdrawal

Opioids include substances that are derived directly from the opium poppy (eg, morphine and codeine); the semisynthetic opioids (eg, heroin);

and the purely synthetic opioids (eg, methadone and fentanyl). In the initial phase of opioid withdrawal, the patient typically experiences a range of symptoms including diarrhea and vomiting, thermoregulation disturbances, insomnia, muscle and joint pain, anxiety, and dysphoria (Table 3). Although these symptoms generally include no life-threatening complications (unlike alcohol withdrawal syndrome), the acute opioid withdrawal syndrome causes marked discomfort and frequently leads to a relapse to drug use [57].

Opioid medications act as agonists at the μ-opioid receptor and cause reduced adrenergic activity at the locus ceruleus. Opioid withdrawal occurs when opioids are abruptly discontinued or when opioid use has diminished. The clinical phenomena associated with opioid withdrawal include neurophysiologic rebound and the central nervous system (CNS) suppression that occurs with opioid use is replaced by CNS hyperactivity [58]. Abrupt opioid withdrawal can be instituted with the administration of naloxone, a complete opiate agonist, in a patient who has recently used opioids, because naloxone binds to the opiate receptor with a greater affinity than do opiate agonists [6]. It is important to remember that opioid withdrawal occurs as part of a physiologic response not only in patients dependent on heroin or prescription opioid medications, but also in patients

Table 3
Clinical manifestations of opioid withdrawal

System	Symptoms
Vitals	Tachycardia
	Fever
	Hypertension
Central nervous system	Restlessness
	Irritability
	Insomnia
	Craving
	Yawning
	Tremor
Eyes	Pupillary dilation
	Lacrimation
Upper respiratory system	Rhinorrhea
	Sneezing
Skin	Piloerection
	Diaphoresis
Gastrointestinal	Nausea
	Vomiting
	Diarrhea
Musculoskeletal	Myalgias
	Arthralgias
	Bone pain

legitimately maintained on opioid medications for the treatment of chronic pain.

The severity of opioid withdrawal varies with the dose and duration of drug use. In addition, route of administration also seems to be important. Data from one study suggest that injection drug use is associated with significantly higher withdrawal symptom scores than was inhaled opioid use [59]. The time to onset of opioid withdrawal symptoms depends on the half-life of the drug being used. For example, withdrawal may begin 4 to 6 hours after the last use of heroin, but up to 36 hours after the last use of methadone [58]. Neuropharmacologic studies of opioid withdrawal have supported the clinical picture of CNS noradrenergic hyperactivity [58,60]. Evidence for the role of noradrenergic hyperactivity in opioid withdrawal has been provided by studies showing elevated norepinephrine metabolite levels [61].

Early findings of opioid withdrawal may include tachycardia and hypertension. Bothersome CNS system symptoms also may occur and include restlessness, irritability, and insomnia. Opioid craving in proportion to the severity of physiologic withdrawal symptoms is typically present. Pupillary dilation can be marked. A variety of cutaneous and mucocutaneous symptoms (including lacrimation; rhinorrhea; and piloerection, also known as ''gooseflesh'') can occur. Patients frequently report yawning and sneezing. Gastrointestinal symptoms, which initially may be mild (anorexia), can progress in moderate to severe withdrawal to include nausea, vomiting, and diarrhea [25,57].

As with the onset of withdrawal, the duration also varies with the half-life of the drug used and the duration of drug use. For example, the meperidine abstinence syndrome, which generally begins 4 to 5 hours after the last dose of meperidine, may peak within 8 to 12 hours and last only 4 to 5 days [58]; whereas heroin withdrawal symptoms, which begin 6 to 8 hours after the last dose of heroin, often peak within 36 to 72 hours and may last for 7 to 14 days [62]. A protracted abstinence syndrome has been described, in which a variety of symptoms may last beyond the typical acute withdrawal period [63]. Findings in prolonged and protracted abstinence may include mild abnormalities in vital signs and continued craving [64].

Management of opioid withdrawal

The choice of pharmacotherapy used to treat opioid withdrawal may be influenced by the presence and severity of patients' underlying medical comorbidities [65]. General supportive measures are necessary for managing withdrawal, and reassuring patients and families that their symptoms are taken seriously.

Substitution with a long-acting opioid in tapering doses is the treatment of choice for managing opioid withdrawal [25]. For short-acting opioids, the natural course of withdrawal generally is relatively brief, but more intense and associated with a higher degree of discomfort than with equivalent

doses of long-acting opioids. It is important to note, however, that there is considerable individual variation. One treatment strategy is to stabilize patients dependent on heroin with methadone, then gradually decrease the methadone dose. Initially, methadone may be given in 5-mg increments as the physical signs of abstinence begin to appear [66], up to a total of 10 to 20 mg over the first 24 hours. Larger methadone doses are required to treat patients who have larger opioid habits; for such patients, a routine starting dose might be 30 rather than 5 mg. Once a stabilizing dose has been reached, methadone is tapered by 20% a day for inpatients, leading to a 1- to 2-week procedure. All patients treated with opioids require close monitoring for treatment effectiveness and toxicity.

α-Adrenergic agonists have also been shown to decrease symptoms of opioid withdrawal. Gold and colleagues [67] reported amelioration of opioid withdrawal symptoms by use of clonidine and postulated that both morphine and clonidine blocked activation of the locus ceruleus, a major noradrenergic nucleus that shows increased activity during opioid withdrawal. Typical doses used to treat opioid withdrawal range between 0.1 and 0.2 mg every 6 hours with close monitoring of blood pressure. Side effects include sedation, dry mouth, orthostatic hypotension, and constipation.

Buprenorphine is a high-affinity, partial agonist at the μ-opioid receptor. Buprenorphine and buprenorphine-naloxone were approved by the US Food and Drug Administration in October 2002 as a pharmacotherapy for opioid dependence [68]. A recent Cochrane systematic review [69] of 18 studies (14 randomized clinical trials) of the use of buprenorphine for opioid withdrawal found that buprenorphine treatment was superior to clonidine and as effective as methadone for ameliorating withdrawal symptoms, treatment retention, and treatment completion. It was also noted in this review that the duration of withdrawal symptoms may be significantly less with buprenorphine compared with methadone [69]. These findings were supported by a subsequent multicenter randomized clinical trial of a 13-day detoxification program using buprenorphine-naloxone versus clonidine [70]. The usual dose of buprenorphine-naloxone required to treat opioid withdrawal symptoms ranges between 8 and 24 mg daily. Therapy with buprenorphine-naloxone should start with a dose of 8 mg and should not begin until symptoms occur and 8 to 24 hours after the last dose of opioid was taken (depending on the half-life of the opioid used). This is because of buprenorphine-naloxone's high receptor affinity, which can precipitate opioid withdrawal if administered while opioids are still bound to the opiate receptor. Limitations to the use of buprenorphine in the treatment of opioid dependence in the ICU are its sublingual administration and issues with regard to pain control and sedation because opioids have little effect in patients receiving buprenorphine because of its high receptor affinity.

In the course of managing opioid withdrawal, clinicians also need to be able to address medical problems seen in this population [71,72]. Such issues

as acute bacterial infections, HIV, and hepatitis C virus–related problems may complicate withdrawal presentation and management. For instance, one study suggests that injection drug use increases cytokine response in patients coinfected with HIV and hepatitis C virus [66].

A recent development in the treatment of opioid dependence is ultrarapid inpatient detoxification from opiates, using sedatives and anesthetics in combination with opiate antagonists. Ultrarapid opiate detoxification first was described in a study of 12 opiate-dependent patients who were given naloxone while under general anesthesia [73]. A more recent study has suggested that ultrarapid opiate detoxification may be no more effective than simpler approaches to the treatment of opioid withdrawal [74,75]. Additionally, safety concerns may limit the usefulness of ultrarapid opiate detoxification [74,75]. Nevertheless, the risks remain considerable and research remains to be done to determine long-term outcomes [73,74,76–78].

Pain control in opioid-dependent patients

Opioid-dependent patients with both acute and chronic pain pose a unique and challenging dilemma to treatment providers. Opioid medications are highly effective for the treatment of both acute and chronic pain and should not necessarily be withheld over concerns regarding current and future abuse. Care needs to be taken, however, to minimize risk of harm [79]. Controversy exists in the literature that the treatment of chronic pain does not necessarily put an individual at risk of the development of opioid addiction because pain is seen as a functional antagonist to the opioid treatment [80]. Data are emerging, however, suggesting that the relationship between opioid treatment of pain and the development of abuse is complex and in need of further study [79,81].

A recent article by Alford and colleagues [82] outlines four common misconceptions regarding treatment of acute pain concurrent with the treatment of opioid dependence: the notions that (1) the medication used for opioid dependence should cover the acute painful condition, (2) use of opioids for analgesia may result in relapse, (3) addition of opioid treatment for acute pain to opioid maintenance for dependence may result in CNS and respiratory depression, and (4) complaints of pain may constitute "drug-seeking" behavior. In general, patients should be maintained on medications to treat opioid dependence (treatment programs should be contacted to verify dose and to ensure easy transition from inpatient hospital stay back to the community) and supplemented with short-acting opioids titrated to pain relief and use of nonopioid medications and techniques to treat pain. In ICU patients, physiologic responses, such as heart rate and blood pressure, may have to be used to monitor pain relief in patients maintained on sedation and mechanical ventilation. It should be recognized that patients with a history of opioid dependence likely exhibit tolerance to opioid medications and may require higher than usual doses to treat pain [82].

Treatment of acute pain in patients maintained on buprenorphine for opioid dependence may be especially challenging. This is because buprenorphine has a higher affinity for the μ-opioid receptor than do opioids. Options in this case include discontinuation of buprenorphine treatment and transition to opioids only or opioids plus methadone; division of daily dose of buprenorphine to three to four times daily to take advantage of pain control properties of the medication; or continuation of buprenorphine and titration of short-acting opioids [82].

Cocaine-related complications

Clinical manifestations of cocaine intoxication

In 2006 in the United States, 1.7 million people reported cocaine abuse or dependence [1]. Cocaine intoxication is characterized by increased adrenergic activity and may present as psychosis (Table 4). Cocaine intoxication also often presents as acute vasospasm and may cause myocardial ischemia or stroke. Additionally, cocaine lowers seizure threshold, and may cause rhabdomyolysis, hyperthermia, and movement disorders.

Management of cocaine intoxication

As with any acute intoxication, the first step in management includes establishment of adequate airway, breathing, and circulation. The toxicity of cocaine ingestion is in large part caused by sympathetic nervous system stimulation. Management consists of blood pressure control and alleviation of any cardiovascular symptoms. A general principle in the management of cocaine intoxication is avoidance of β-blocking agents [83]. Use of these agents may cause an unopposed α-adrenergic effect, which may in turn worsen symptoms. The psychomotor agitation associated with cocaine intoxication can usually be managed with benzodiazepines and other supportive measures.

Clinical manifestations of cocaine withdrawal

Cocaine withdrawal is characterized by depressed mood and any two of the following: fatigue, vivid dreams, sleep disturbance, increased appetite, psychomotor retardation, or agitation [84]. These symptoms are a result of depleted dopamine stores.

Management of cocaine withdrawal

Manifestations of cocaine intoxication, rather than cocaine withdrawal, are more likely to get the attention of a critical care team [6]. For patients presenting with suspected cocaine-induced vasospasm, avoidance of the use of β-blockers, which may promote an unopposed α-effect, is the general rule. Cocaine withdrawal is typically mild and treated with supportive care and treatment of complications.

Several interventions have been studied for the treatment of cocaine dependence. These include γ-aminobutyric acid–acting agents including gabapentin and tiagabine; dopaminergic agents including bromocriptine and amantadine; immunotherapies; and propranolol, although its use might aggravate vasospasm [84–86].

Benzodiazepine-related complications

Clinical manifestations of benzodiazepine intoxication

The clinical manifestations of benzodiazepine overdose include slurred speech, incoordination, confusion, unsteady gait, and impaired memory and concentration (see Table 4). Severe intoxication can lead to stupor or coma. It is important to recognize that symptoms of benzodiazepine intoxication are very nonspecific and can easily be confused with other substance intoxication or medical problems.

Management of benzodiazepine intoxication

Initial management of benzodiazepine intoxication includes general supportive and resuscitative measures. Treatment with the benzodiazepine antagonist, flumazenil, should be considered in patients in whom benzodiazepine overdose is likely [87,88]. The starting dose of flumazenil is 0.2 mg intravenously over 30 minutes. Flumazenil should not, however, be routinely given to all patients presenting with nonspecific symptoms that may represent benzodiazepine intoxication. This is because use of flumazenil may induce seizures in patients with benzodiazepine dependence; because it may uncover other dangerous symptoms in patients with mixed substance overdose; and because of the nonspecific nature of benzodiazepine intoxication syndrome, it may be administered inappropriately.

Clinical manifestations of benzodiazepine withdrawal

Benzodiazepine withdrawal, similar to alcohol withdrawal, is characterized by autonomic hyperactivity and can result in seizures [25]. Clinical manifestations often occur between 2 and 10 days after abrupt withdrawal of the benzodiazepine. Increased anxiety and irritability may be a salient feature of this syndrome [6]. The severity and duration of withdrawal symptoms depend in part on the half-life of the medication being used. The benzodiazepine withdrawal syndrome can be precipitated by administration of flumazenil to patients taking benzodiazepines [89].

Management of benzodiazepine withdrawal

Withdrawal from benzodiazepines follows the same treatment protocol as for alcohol withdrawal. Treatment generally consists of use of a long-acting benzodiazepine in tapering doses over time. The symptom-triggered approach has been shown to be as effective as the fixed-dose approach for

Table 4
Manifestations and treatment of intoxication and withdrawal of certain substances of abuse

Substance	Signs or symptoms of intoxication or withdrawal	Treatment
Cocaine	Intoxication	Supportive management
	Myocardial ischemia	Avoidance of β-blockers
	Stroke	
	Rhabdomyolosis	
	Hyperthermia	
	Seizures	
	Hypertension	
	Withdrawal	Use of benzodiazepines
	Depression mood	Supportive care
	Fatigue	
	Vivid dreams	
	Sleep disturbance	
	Psychomotor retardation or agitation	
Benzodiazepines	Intoxication	Supportive management
	Slurred speech	Consider administration of flumazenil
	Unsteady gait	
	Impaired memory or attention	
	Confusion	
	Stupor	
	Coma	
	Withdrawal	Substitution of a long-acting benzodiazepine in tapering doses with use of a symptom-triggered approach
	Autonomic hyperactivity	
	Seizures	
	Anxiety	
	Irritability	
Marijuana	Withdrawal	Supportive care
	Anger	
	Aggression	
	Anxiety	
	Irritability	
	Insomnia	
Nicotine	Withdrawal	Supportive care
	Sweating	
	Frequent urination	
	Gastrointestinal disturbances	
	Drowsiness	
	Bradycardia	
Hallucinogens	Intoxication	Supportive care
	Hallucinations or derealization	
	Pupillary dilation	
	Tachycardia	
	Sweating	
	Palpitations	
	Blurred vision	
	Tremors	
	Uncoordination	
	Withdrawal	Urinary acidification
	Flashbacks	Supportive care
	Anxiety	
	Depression	

Table 4
(*continued*)

Substance	Signs or symptoms of intoxication or withdrawal	Treatment
Methamphetamines	Intoxication	Supportive care
	Diaphoresis	
	Hypertension	
	Tachycardia	
	Agitation	
	Psychosis	
	Withdrawal	Supportive care
	Fatigue	
	Irritability	
	Insomnia or sleep disturbance	
	Psychotic reactions	
	Anxiety	

the treatment of benzodiazepine withdrawal [90]. Studies also suggest that the use of carbamazepine is effective in the treatment of benzodiazepine withdrawal. The medication must be administered for at least 2 weeks time, however, and then gradually tapered [25].

Marijuana and nicotine withdrawal

Withdrawal syndromes from marijuana and nicotine are generally considered mild (see Table 4). Marijuana withdrawal is characterized by anger, aggression, anxiety, irritability, and insomnia [22]. Nicotine withdrawal is associated with sweating, frequent urination, gastrointestinal disturbances, drowsiness, and bradycardia [23]. Treatment for both consists of supportive care. For nicotine withdrawal, however, transdermal nicotine can be administered, although a recent case control study suggests an association between administration of nicotine replacement therapy in the ICU with increased mortality [91].

Relevant issues and complications regarding substance use

It is important to notice that patients with substance abuse often have underlying psychiatric comorbidities, including mood disorders. Screening for and treatment of psychiatric disorders is an essential part of treatment of the underlying substance abuse [25]. Additionally, screening for abuse of or dependence on other substances is necessary to treatment planning.

Comprehensive substance abuse treatment planning is essential to the care of patients with substance abuse issues. It is not adequate to care for patients with substance use and withdrawal without facilitating referral

for long-term care after the initial critical care and inpatient hospitalization phase [9,65]. It is up to the medical team caring for patients to have an understanding of the resources available in the surrounding community. Appropriate referral sources include detoxification facilities, counseling services, and area 12-step programs [92].

Iatrogenic dependence

Patients with critical illness often require prolonged stays in the ICU and large cumulative doses of opioids and sedatives to facilitate pain control, anxiety, and sedation. Acute withdrawal syndromes may present in patients receiving opioids or benzodiazepines as a result of rapid weaning for transitions to lower levels of care. Continuous infusions of opioids or benzodiazepines may place patients at higher risk for the development of acute withdrawal than would administration of these medications by bolus injection [6]. It is up to the critical care team to consider implementation of weaning protocols, consisting of a 5% to 10% reduction per day, early on in the course of a patient's ICU stay [93].

Summary

Substance use and withdrawal are common among patients presenting to the ICU with critical illness and may complicate the treatment course. It is important for the critical care team to consider underlying substance use disorders and withdrawal syndromes in patients presenting for care. It may be difficult to obtain a history of these disorders as a result of altered mental status and a patient's family should also be asked. Additionally, it is important to consider polysubstance use in any patient presenting with a substance use issue.

General principles regarding the treatment of substance intoxication and withdrawal include application of general resuscitative measures including airway, breathing, and circulatory management. For specific withdrawal syndromes, substitution of a long-acting agent (which acts on the same receptor pathway as the misused substance) in tapering doses is the general rule. Additionally, use of a symptom-triggered approach to the treatment of substance withdrawal decreases length of stay and cumulative medication administered. Of the utmost importance is long-term planning and referral for patients with underlying substance use disorders to allow for the best chances for successful treatment of these debilitating, chronic conditions.

Appendix 1

Clinical Institute Withdrawal Assessment for Alcohol Scale-Revised[1]

Nausea/Vomiting - Rate on scale 0 – 7 0 – None 1 - Mild nausea with no vomiting 2 3 4 - Intermittent nausea 5 6 7 - Constant nausea and frequent dry heaves and vomiting	**Tremors -** have patient extend arms & spread fingers. Rate on scale 0 – 7. 0 - No tremor 1 - Not visible, but can be felt fingertip to fingertip 2 3 4 - Moderate, with patient's arms extended 5 6 7 - severe, even w/ arms not extended
Anxiety - Rate on scale 0 – 7 0 - no anxiety, patient at ease 1 - mildly anxious 2 3 4 - moderately anxious or guarded, so anxiety is inferred 5 6 7 - equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions.	**Agitation** - Rate on scale 0 – 7 0 - normal activity 1 - somewhat normal activity 2 3 4 - moderately fidgety and restless 5 6 7 - paces back and forth, or constantly thrashes about
Paroxysmal Sweats - Rate on Scale 0 – 7. 0 - no sweats 1- barely perceptible sweating, palms moist 2 3 4 - beads of sweat obvious on forehead 5 6 7 - drenching sweats	**Orientation and clouding of sensorium** - Ask, "What day is this? Where are you? Who am I?" Rate scale 0 – 4 0 – Oriented 1 – cannot do serial additions or is uncertain about date 2 - disoriented to date by no more than 2 calendar days 3 - disoriented to date by more than 2 calendar days 4 - Disoriented to place and / or person
Tactile disturbances - Ask, "Have you experienced any itching, pins & needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?" 0 - none 1 - very mild itching, pins & needles, burning, or numbness 2 - mild itching, pins & needles, burning, or numbness 3 - moderate itching, pins & needles, burning, or numbness 4 - moderate hallucinations 5 - severe hallucinations 6 - extremely severe hallucinations 7 - continuous hallucinations	**Auditory Disturbances** - Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?" 0 - not present 1 - Very mild harshness or ability to startle 2 - mild harshness or ability to startle 3 - moderate harshness or ability to startle 4 - moderate hallucinations 5 - severe hallucinations 6 - extremely severe hallucinations 7 - continuous hallucinations
Visual disturbances - Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you or that you know isn't there?" 0 - not present 1 - very mild sensitivity 2 - mild sensitivity 3 - moderate sensitivity 4 - moderate hallucinations 5 - severe hallucinations 6 - extremely severe hallucinations 7 - continuous hallucinations	**Headache** - Ask, "Does your head feel different than usual? Does it feel like there is a band around your head?" Do not rate dizziness or lightheadedness. 0 - not present 1 - very mild 2 – mild 3 – moderate 4 - moderately severe 5 – severe 6 - very severe 7 - extremely severe

[1] Note. Total score 67. Protocols should be tailored to consider a cut-off score to administer PRN medications only (eg, ≥ 8) and PRN medications added to scheduled medication (eg, ≥ 15).

References

[1] Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2006 National Survey on Drug Use and Health: National Findings 2007. Report No.: Office of Applied Studies, DHHS Publication No. SMA 07–4293.
[2] Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000 [see comment][erratum appears in JAMA. 2005 Jan 19;293(3):293–4; PMID: 15657315]. JAMA 2004;291(10):1238–45.
[3] McCabe S. Substance use and abuse in trauma: implications for care. Crit Care Nurs Clin North Am 2006;18(3):371–85.
[4] Borges G, Mondragon L, Medina-Mora ME, et al. A case-control study of alcohol and substance use disorders as risk factors for non-fatal injury. Alcohol Alcohol 2005;40(4): 257–62.
[5] Chisholm D, Doran C, Shibuya K, et al. Comparative cost-effectiveness of policy instruments for reducing the global burden of alcohol, tobacco and illicit drug use. Drug Alcohol Rev 2006;25(6):553–65.
[6] Jenkins DH. Substance abuse and withdrawal in the intensive care unit: contemporary issues. Surg Clin North Am 2000;80(3):1033–53.
[7] Cherpitel CJ. Alcohol and injuries: a review of international emergency room studies since 1995. Drug Alcohol Rev 2007;26(2):201–14.
[8] Hadfield RJ, Mercer M, Parr MJ. Alcohol and drug abuse in trauma. Resuscitation 2001; 48(1):25–36.
[9] Gentilello LM. Alcohol and injury: American College of Surgeons Committee on trauma requirements for trauma center intervention. Journal of Trauma-Injury Infection & Critical Care 2007;62(Suppl 6):S44–5.
[10] Dinh-Zarr T, Goss C, Heitman E, et al. Interventions for preventing injuries in problem drinkers [update of Cochrane Database Syst Rev 2000;(2):CD001857; PMID: 10796829]. Cochrane Database Syst Rev 2004;(3):CD001857.
[11] Macdonald S, Anglin-Bodrug K, Mann RE, et al. Injury risk associated with cannabis and cocaine use. Drug Alcohol Depend 2003;72(2):99–115.
[12] Moss M, Burnham EL. Alcohol abuse in the critically ill patient [see comment]. Lancet 2006; 368(9554):2231–42.
[13] Moss M, Parsons PE, Steinberg KP, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med 2003;31(3):869–77.
[14] Esper A, Burnham EL, Moss M. The effect of alcohol abuse on ARDS and multiple organ dysfunction. Minerva Anestesiol 2006;72(6):375–81.
[15] Al-Sanouri I, Dikin M, Soubani AO. Critical care aspects of alcohol abuse. South Med J 2005;98(3):372–81.
[16] Zapantis A, Leung S. Tolerance and withdrawal issues with sedation. Crit Care Nurs Clin North Am 2005;17(3):211–23.
[17] Spies CD, Dubisz N, Neumann T, et al. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. Crit Care Med 1996;24(3):414–22.
[18] Koch-Weser J, Sellers EM, Kalant H. Alcohol intoxication and withdrawal. N Engl J Med 1976;294(14):757–62.
[19] O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients [see comment]. Ann Intern Med 2000;133(1):40–54.
[20] Pilotte NS. Neurochemistry of cocaine withdrawal. Curr Opin Neurol 1997;10(6):534–8.
[21] Denis C, Fatseas M, Lavie E, et al. Pharmacological interventions for benzodiazepine monodependence management in outpatient settings. Cochrane Database Syst Rev 2006;(3): CD005194.

[22] Budney AJ, Moore BA, Vandrey RG, et al. The time course and significance of cannabis withdrawal. J Abnorm Psychol 2003;112(3):393–402.
[23] Padula C, Willey C. Tobacco withdrawal in CCU patients. Dimens Crit Care Nurs 1993; 12(6):305–12.
[24] Wax PM, et al. Withdrawal syndromes. In: Rippe JM, Irwin RS, Fink MP, et al, editors. Intensive care medicine. 3rd edition. Boston: Little, Brown, and company; 1996. p. 1718–26.
[25] Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal [see comment]. N Engl J Med 2003;348(18):1786–95.
[26] Ballenger JC, Post RM. Kindling as a model for alcohol withdrawal syndromes. Br J Psychiatry 1978;133:1–14.
[27] Linnoila M, Mefford I, Nutt D, et al. NIH conference: alcohol withdrawal and noradrenergic function. Ann Intern Med 1987;107(6):875–89.
[28] Etherington JM. Emergency management of acute alcohol problems. Part 1: uncomplicated withdrawal [see comment]. Can Fam Physician 1996;42:2186–90.
[29] Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. CNS Drugs 2003;17(14):1013–30.
[30] Rathlev NK, Ulrich AS, Delanty N, et al. Alcohol-related seizures. J Emerg Med 2006;31(2): 157–63.
[31] Turner RC, Lichstein PR, Peden JG Jr, et al. Alcohol withdrawal syndromes: a review of pathophysiology, clinical presentation, and treatment [see comment]. J Gen Intern Med 1989;4(5):432–44.
[32] Tsuang JW, Irwin MR, Smith TL, et al. Characteristics of men with alcoholic hallucinosis [see comment]. Addiction 1994;89(1):73–8.
[33] Merrin EL. Withdrawal states and alcoholic hallucinosis. Am J Psychiatry 1980;137(10): 1280–1.
[34] Ferguson JA, Suelzer CJ, Eckert GJ, et al. Risk factors for delirium tremens development. J Gen Intern Med 1996;11(7):410–4.
[35] Abraham E, Shoemaker WC, McCartney SF. Cardiorespiratory patterns in severe delirium tremens. Arch Intern Med 1985;145(6):1057–9.
[36] DeBellis R, Smith BS, Choi S, et al. Management of delirium tremens. J Intensive Care Med 2005;20(3):164–73.
[37] Pearce JMS. Wernicke-Korsakoff encephalopathy. Eur Neurol 2008;59(1–2):101–4.
[38] O'Brien JM Jr, Lu B, Ali NA, et al. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients [see comment]. Crit Care Med 2007;35(2):345–50.
[39] Mayo-Smith MF. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal [see comment]. JAMA 1997; 278(2):144–51.
[40] Weinberg JA, Magnotti LJ, Fischer PE, et al. Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. Journal of Trauma-Injury Infection & Critical Care 2008;64(1):99–104.
[41] Adinoff B. Double-blind study of alprazolam, diazepam, clonidine, and placebo in the alcohol withdrawal syndrome: preliminary findings. Alcohol Clin Exp Res 1994;18(4): 873–8.
[42] Kaim SC, Klett CJ, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. Agressologie 1968;9(2):305–8.
[43] Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse: withdrawal and treatment. Med Clin North Am 1997;81(4):881–907.
[44] Saitz R, Mayo-Smith MF, Roberts MS, et al. Individualized treatment for alcohol withdrawal: a randomized double-blind controlled trial [see comment]. JAMA 1994; 272(7):519–23.

[45] DeCarolis DD, Rice KL, Ho L, et al. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy 2007;27(4): 510–8.
[46] Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Br J Addict 1989; 84(11):1353–7.
[47] Stuppaeck CH, Barnas C, Falk M, et al. Assessment of the alcohol withdrawal syndrome: validity and reliability of the translated and modified Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-A). Addiction 1994;89(10):1287–92.
[48] Maldonado JR, Brooks JO, Nguyen LH, et al. A comparison of lorazepam versus diazepam in the treatment of alcohol withdrawal. Submitted.
[49] Hecksel KA, Bostwick JM, Jaeger TM, et al. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. Mayo Clin Proc 2008;83(3):274–9.
[50] Kraus ML, Gottlieb LD, Horwitz RI, et al. Randomized clinical trial of atenolol in patients with alcohol withdrawal. N Engl J Med 1985;313(15):905–9.
[51] Stuppaeck CH, Pycha R, Miller C, et al. Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. Alcohol Alcohol 1992;27(2):153–8.
[52] Spies CD, Otter HE, Huske B, et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003;29(12):2230–8.
[53] Riihioja P, Jaatinen P, Haapalinna A, et al. Effects of dexmedetomidine on rat locus coeruleus and ethanol withdrawal symptoms during intermittent ethanol exposure. Alcohol Clin Exp Res 1999;23(3):432–8.
[54] Baddigam K, Russo P, Russo J, et al. Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. J Intensive Care Med 2005;20(2):118–23.
[55] Maccioli GA. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology 2003;98(2): 575–7.
[56] Rovasalo A, Tohmo H, Aantaa R, et al. Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. Gen Hosp Psychiatry 2006;28(4):362–3.
[57] O'Connor PG, Kosten TR, Stine SM. Management of opioid intoxication and withdrawal. In: Graham AW, Schultz TK, Mayo-Smith MF, et al, editors. Principles of addiction medicine. 3rd edition. Chevy Chase (MD): American Society of Addiction Medicine; 2003. p. 651–68.
[58] Jaffe JH. Drug addiction and drug abuse. In: Gilman AG, Rall TW, Nies AS, et al, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th edition. New York: Pergamon Press; 1990. p. 522–73.
[59] Smolka M, Schmidt LG. The influence of heroin dose and route of administration on the severity of the opiate withdrawal syndrome. Addiction 1999;94(8):1191–8.
[60] Gunne LM. Noradrenaline and adrenaline in the rat brain during acute and chronic morphine administration and during withdrawal. Nature 1959;184(Suppl 25):1950–1.
[61] Crawley JN, Laverty RN, Roth RH. Clonidine reversal of increased norepinephrine metabolite levels during morphine withdrawal. Eur J Pharmacol 1979;57:247–55.
[62] Dole VP. Narcotic addiction: physical dependence and relapse. N Engl J Med 1972;286(18): 988–92.
[63] Schuckit MA. Opiates and other analgesics. Drug and alcohol abuse: a clinical guide to diagnosis and treatment. 3rd edition. New York: Plenum Publishing Company; 1988. p. 118–42.
[64] Wen HL, Ho WK, Wen PY. Comparison of the effectiveness of different opioid peptides in suppressing heroin withdrawal. Eur J Pharmacol 1984;100(2):155–62.
[65] O'Connor PG, Samet JH, Stein MD. Management of hospitalized intravenous drug users: role of the internist. Am J Med 1994;96(6):551–8.
[66] Graham CS, Wells A, Edwards EM, et al. Effect of exposure to injection drugs or alcohol on antigen-specific immune responses in HIV and hepatitis C virus coinfection. J Infect Dis 2007;195(6):847–56.

[67] Gold M, Redmond DE, Kleber HD. Clonidine blocks acute opiate withdrawal symptoms. Lancet 1978;2:599–600.
[68] Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. Ann Intern Med 2002;137(8):688–92.
[69] Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal [update of Cochrane Database Syst Rev 2004;(4):CD002025; PMID: 15495026]. Cochrane Database Syst Rev 2006;(2):CD002025.
[70] Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network [see comment][erratum appears in Addiction. 2006 Sep;101(9):1374]. Addiction 2005;100(8):1090–100.
[71] O'Connor PG, Selwyn PA, Schottenfeld RS. Medical care for injection-drug users with human immunodeficiency virus infection [see comment]. N Engl J Med 1994;331(7):450–9.
[72] Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later [see comment]. Ann Intern Med 1993;119(10):1017–28.
[73] Loimer N, Schmid R, Presslich O, et al. Naloxone treatment for opiate withdrawal syndrome. Br J Psychiatry 1988;153:851–2.
[74] Collins ED, Kleber HD, Whittington RA, et al. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial [see comment]. JAMA 2005;294(8):903–13.
[75] O'Connor PG. Methods of detoxification and their role in treating patients with opioid dependence [see comment][comment]. JAMA 2005;294(8):961–3.
[76] Loimer N, Schmid R, Lenz K, et al. Acute blocking of naloxone-precipitated opiate withdrawal symptoms by methohexitone. Br J Psychiatry 1990;157:748–52.
[77] Scherbaum N, Klein S, Kaube H, et al. Alternative strategies of opiate detoxification: evaluation of the so-called ultra-rapid detoxification. Pharmacopsychiatry 1998;31(6): 205–9.
[78] O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques [see comment]. JAMA 1998;279(3):229–34.
[79] Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend 2006;81(2):103–7.
[80] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986;25(2):171–86.
[81] Forge KS. Opioid dependence and addiction during opioid treatment of chronic pain [see Ballantyne JC, Lacomment][erratum appears in Pain. 2007 Oct;131(3):350]. Pain 2007; 129(3):235–55.
[82] Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy [erratum appears in Ann Intern Med. 2006 Mar 21;144(6):460]. Ann Intern Med 2006;144(2):127–34.
[83] Lange RA, Cigarroa RG, Yancy CW Jr, et al. Cocaine-induced coronary-artery vasoconstriction [see comment]. N Engl J Med 1989;321(23):1557–62.
[84] Sofuoglu M, Poling J, Gonzalez G, et al. Cocaine withdrawal symptoms predict medication response in cocaine users. Am J Drug Alcohol Abuse 2006;32(4):617–27.
[85] Kampman KM, Dackis C, Lynch KG, et al. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. Drug Alcohol Depend 2006;85(2): 129–37.
[86] Sofuoglu M, Kosten TR. Novel approaches to the treatment of cocaine addiction. CNS Drugs 2005;19(1):13–25.
[87] Lheureux P, Vranckx M, Leduc D, et al. Flumazenil in mixed benzodiazepine/tricyclic antidepressant overdose: a placebo-controlled study in the dog. Am J Emerg Med 1992; 10(3):184–8.

[88] Weinbroum AA, Flaishon R, Sorkine P, et al. A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. Drug Saf 1997;17(3):181–96.
[89] Ngo AS, Anthony CR, Samuel M, et al. Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? Resuscitation 2007;74(1):27–37.
[90] McGregor C, Machin A, White JM. In-patient benzodiazepine withdrawal: comparison of fixed and symptom-triggered taper methods. Drug Alcohol Rev 2003;22(2):175–80.
[91] Lee AH, Afessa B. The association of nicotine replacement therapy with mortality in a medical intensive care unit [see comment]. Crit Care Med 2007;35(6):1517–21.
[92] D'Onofrio G, Becker B, Woolard RH. The impact of alcohol, tobacco, and other drug use and abuse in the emergency department. Emerg Med Clin North Am 2006;24(4):925–67.
[93] Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients [see comment]. Crit Care Med 1998;26(4):676–84.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 789–856

CRITICAL
CARE
CLINICS

Pathoetiological Model of Delirium: a Comprehensive Understanding of the Neurobiology of Delirium and an Evidence-Based Approach to Prevention and Treatment

José R. Maldonado, MD, FAPM, FACFE

Departments of Psychiatry and Medicine, Stanford University School of Medicine, 401 Quarry Road, Suite 2317, Stanford, CA 94305, USA

> "We thus arrive at the proposition that a derangement in functional metabolism underlies all instances of delirium and that this is reflected at the clinical level by the characteristic disturbance in cognitive functions." (Engel and Romano, 1959)

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances [1–3]. The literature describes the sensorium of delirious patients as "waxing and waning." On the other hand, it is actually alertness (ie, a state of readiness of an organism to integrate stimuli enabling possible responses to stimuli) and vigilance (ie, paying attention to crucial external events) that are fluctuating. A delirious patient does indeed receive external information but integrates it incorrectly, which produces behavioral responses that are inadequate to the environment. So it is not really the attention, but the mental content that is altered and fluctuating.

The incidence of delirium is rather high in both medically and surgically ill patients [4,5], and even higher among critically ill patients (up to 80%) [6,7]. In addition to causing distress to patients, families, and medical caregivers, the development of delirium has been associated with increased

Parts of the article were presented at the annual meetings of the Academy of Psychosomatic Medicine, Fort Myers, FL, November 9, 2004; the Canadian Academy of Psychosomatic Medicine (CAPM), Toronto, Canada. November 10, 2006; and. U.S. Psychiatric Congress & Mental Health Congress, Orlando, Florida, October 12, 2007.

E-mail address: jrm@stanford.edu

doi:10.1016/j.ccc.2008.06.004 *criticalcare.theclinics.com*

morbidity and mortality [8–12], increased cost of care [11,13], increased hospital-acquired complications [12], poor functional and cognitive recovery [4,10,14], decreased quality of life [12,14,15], prolonged hospital stays [6,8,10–12,14–16], and increased placement in specialized intermediate- and long-term care facilities [12,14,15]. Contrary to some definitions, delirium is unfortunately not always reversible. A study conducted at a teaching hospital suggested that once delirium occurs, only about 4% of patients experience full resolution of symptoms before discharge from the hospital [10]. In the same study, it was not until 6 months after hospital discharge that an additional 40% experienced full resolution of symptoms.

To date, no single cause of delirium has been identified. Known risk factors for delirium include advanced age, preexisting cognitive impairment, medications (especially those with high anticholinergic potential), sleep deprivation, hypoxia and anoxia, metabolic abnormalities, and a history of alcohol or drug abuse. Over time, a number of theories have been proposed in an attempt to explain the processes leading to the development of delirium. Most of these theories are complementary, rather than competing. The ''oxygen deprivation hypothesis'' proposes that decreased oxidative metabolism in the brain causes cerebral dysfunction because of abnormalities of various neurotransmitter systems. The ''neurotransmitter hypothesis'' suggests that reduced cholinergic function; excess release of dopamine, norepinephrine, and glutamate; and both decreased and increased serotonergic and gamma-aminobutyric acid activity may underlie the different symptoms and clinical presentations of delirium. The ''neuronal aging hypothesis'' is closely related to the changes in neurotransmitters observed in normal aging. Accordingly, this theory suggests that elderly patients are more at risk for developing delirium, likely because of age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems. The ''inflammatory hypothesis'' suggests that increased cerebral secretion of cytokines as a result of a wide range of physical stresses may lead to the development of delirium, probably by their effect on the activity of various neurotransmitter systems. The ''physiologic stress hypothesis'' suggests that trauma, severe illness, and surgery may give rise to modification of blood-brain barrier permeability, to the sick euthyroid syndrome with abnormalities of thyroid hormone concentrations, and to an increased activity of the hypothalamic-pituitary-adrenal axis. These circumstances may alter neurotransmitter synthesis and cause the release of cytokines in the brain, thus contributing to the occurrence of delirium. Finally, the ''cellular-signaling hypothesis'' suggests that more fundamental processes like intraneuronal signal transduction (ie, second messenger systems that at the same time use neurotransmitters as first messengers) may be disturbed, affecting therefore neurotransmitter synthesis and release. It is likely that none of these theories by themselves explain the phenomena of delirium, but rather it is more likely that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium (Table 1). At the end, it is unlikely that

Table 1
Theorized neurochemical mechanisms associated with conditions leading to delirium

Delirium source	ACH	DA	GLU	GABA	5HT	NE	Trp	Phe	His	Cytok	HPA axis	NMDA activity	Chages in RBF	EEG	Mel	Inflam	Cort
Anoxia/hypoxia	↓	↑	↑	↓	↓	↓	↑?	↑	↑, ↓	⫩↑	⫩	↑	⫩	↓		↑	
Aging	↓									⫩↑	⫩		⫩	↓			
CVA		↑														⫩	↑
Hepatic Failure	↓	↑	↑	↑	↑	↓?	↑	↑			⫩	↑	⫩	↓			
Sleep deprivation			⫩								⫩			↓	⫩,↓	⫩	↑
Trauma, Sx, and post-op	↓	↑?			↓	↑?	↓	↑	↑	↑	↑		⫩	↓	↓	↑	↑
Etoh and CNS-Dep withdrawal	↑?	↑?	↑	↓	↓, ↑	↑	↓				⫩		⇔	↑	↓		↑
DA agonist		↑			↓	↑?					⫩						
Infection/Sepsis	↓?	↑?			↓		↓	↓	↓	↑	⫩		⫩			↑	↑
GABA use	↓			↑							⫩				↓		
Dehydration and electrolyte imbalance	↓?		↑							↑	⫩						
Glucocorticoids																	↑
Medical illness	↓				↓		↓	↑					⫩		↓	⫩	↑
Hypoglyemia	↓																

Abbreviations: ↑, likely to be increased or activated; ↓, likely to be decreased; ⇔, no significant changes; ⫩, likely a contributor, exact mechanism is unclear; 5HT, 5-hydroxytryptamine or serotonin; ACH, acetylcholine; CNS-Dep, central nervous system depressant agent; Cort, Cortisol; CVA, cerebro-vascular accident; Cytok, cytokines; DA, dopamine; EEG, electroencephalograph; Etoh, alcohol; GABA, gamma-aminobutyric acid; GLU, glutamate; His, histamine; HPA axis, hypothalamic-pituitary-adrenocortical axis; Mel, melatonin; Inflam, inflammation; NE, norepinephrine; NMDA, N-methyl-D-aspartic acid; Phe, phenylalanine; RBF, regional blood flow; Sx, surgery; Trp, tryptophan.

we find a stringently common pathway to the development of delirium, more likely, the syndromes of delirium (ie, hyper, hypo, and mixed types) represent the common end product of one or various independent neurochemical pathways (Table 2).

This article is an attempt to understand the pathophysiological contributors to delirium and their relationship regarding basic neurotransmitter pathways and systems. The author will describe our interpretation of the cascade of processes that lead to delirium based on a comprehensive review of the literature (Fig. 1). Throughout the article we shall discuss the different neurochemical mechanisms and pathways that lead to the common features of delirium. Finally, based on those theories and understanding, we can begin postulating potential prevention methods and treatment techniques.

The neurochemical pathways of delirium

Aging: acetylcholine, vascular supply, and delirium

Human studies have revealed that the cholinergic system is widely involved in arousal, attention, memory, and rapid-eye-movement (REM) sleep. A deficiency of cholinergic function relative to that of other neurotransmitters can be expected to alter the efficiency of these mental mechanisms [17]. In fact, one leading hypothesis is that delirium results from an impairment of central cholinergic transmission [18–20]. Low levels of acetylcholine (ACh) in plasma and cerebrospinal fluid (CSF) have been described in delirious patients [18,21–28].

Studies have suggested that age is an independent predictor of transitioning to delirium. Some have demonstrated that older patients have a higher incidence of developing postoperative delirium, even after relatively simple outpatient surgery [29]. In fact, for each additional year after age 65, the probability of transitioning to delirium increased by 2% (multivariable P values less than .05) [30]. Studies evaluating pre- and

Table 2
Neurochemical mechanisms associated with delirium type

Delirium type	ACH	DA	GLU	GABA	5HT	NE	O2	Sleep deprivation	Cytokines	HPA	Trp	Phe	EEG	Mel
Hypo	↓	↑	↑		↑	↓		↑		↑	↑	↑	↓	
Hyper	↓		↑		↓	↓		↑		↑	↑	↑	↑	↓
Mixed	↓		↑			↓		↑		↑	↑	↑	↑↓	

Abbreviations: ↑, likely to be increased; ↓, likely to be decreased; ⇔, uncertain action; 5HT, 5-hydroxytryptamine or serotonin; ACH, acetylcholine; DA, dopamine; EEG, electroencephalograph; GABA, gamma-aminobutyric acid; GLU, glutamate; HPA, hypothalamic-pituitary-adrenocortical axis; Mel, melatonin; NE, norepinephrine; Phe, phenylalanine; Sx, surgery; Trp, tryptophan.

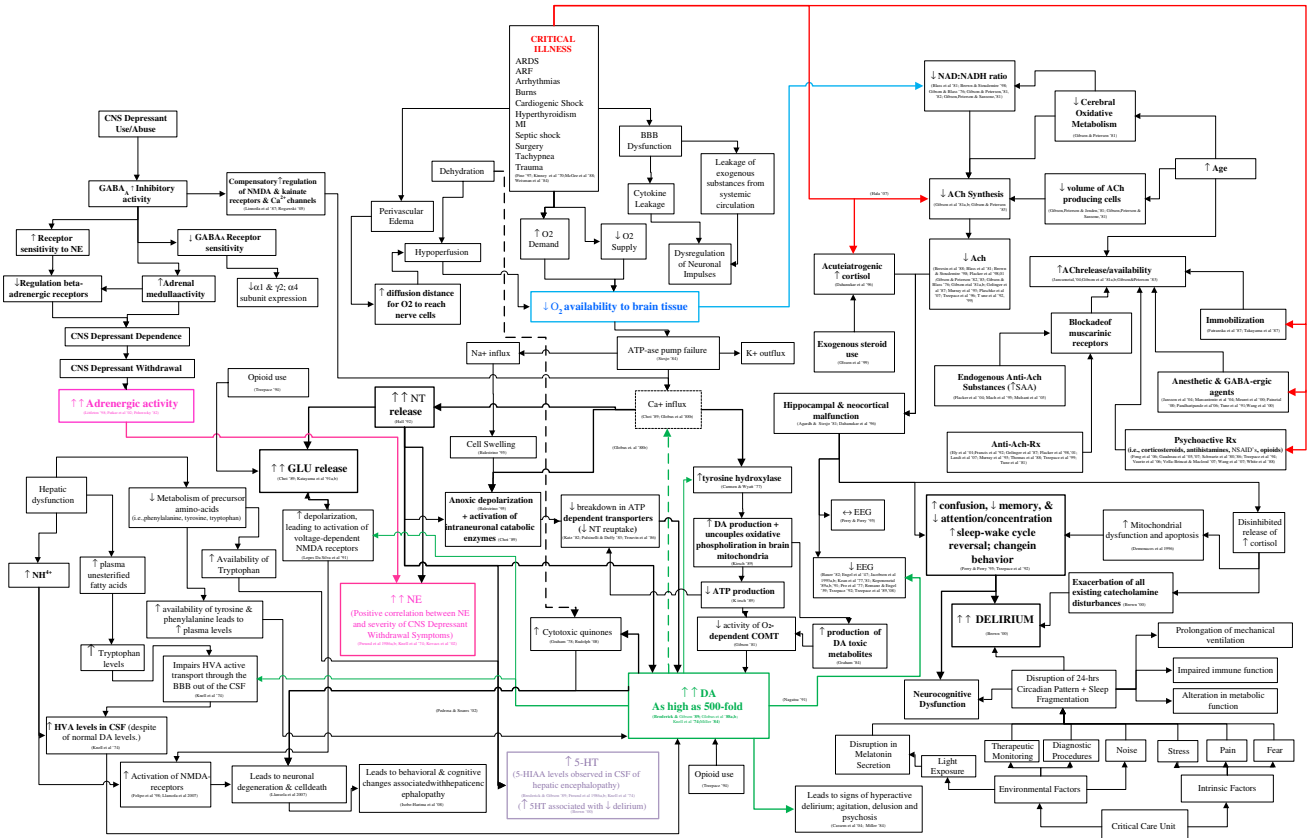

Fig. 1. A basic pathoetiological model of delirium.

postoperative neuropsychological performance in older nondemented patients after elective orthopedic surgery found that the presence of preoperative attentional deficits was closely associated with postoperative delirium [31].

The increased incidence of delirium in older patients may be associated with a decrease in the volume of Ach-producing cells occurring during the normal aging process [32]. Aging is also associated with decreased cerebral oxidative metabolism [33]. Both of these factors lead to a normal decline in ACh synthesis [32–35]. The decline in cognitive functioning associated with the normal process of aging may be aggravated by the presence of even mild hypoxia, which further inhibits ACh synthesis and its release [17,36,37]. Hypoxia leads to decreased oxygen supply to brain tissue, which leads to a decreased redox state (nicotinamide adenine dinucleotide [NAD]-oxidized: NADH-reduced), which may also result in decreased ACh production [17,33,36–39].

Similarly, studies in both the acute medical ward and surgical units suggest that the presence of baseline dementia increases the occurrence of delirium [40–42]. Alzheimer's disease, which is characterized by a loss of cholinergic neurons, carries an increased risk of delirium, particularly associated with the use of anticholinergic medication [33].

Higher levels for serum anticholinergic activity (SAA) [43] have been associated with an increased likelihood of delirium in both surgical [23,44,45] and medical [18,46] inpatients. A dose-response relationship between symptoms of delirium and SAA has also been suggested [18]. Studies have shown that SAA is significantly higher in delirious, compared with nondelirious patients, and that resolving delirium is correlated with decreasing SAA [47]. In fact, some have observed that high SAA (ie, >20) has a predictive value for delirium (defined as confusion assessment method [CAM] positive) of 100% [48].

Most clinicians had presumed this high association between SAA and delirium to be the result of the use of exogenous anticholinergic substances. Nevertheless, studies have demonstrated that detectable SAA levels in serum have been found in delirious patients who were not exposed to pharmacologic agents with known anticholinergic activity. These findings suggest that endogenous anticholinergic substances may exist during acute illness and may be implicated in the etiology of delirium [22,47,49].

Animal studies have demonstrated the negative influence of age on prefrontal ACh release and Fos (ie, Fos protein) response in the hypothalamic paraventricular nucleus and the nucleus tractus solitarius (NTS) of rats following isoflurane anesthesia (known to decrease ACh release in most brain regions). The old rat group showed significantly greater Fos induction in the paraventricular nucleus compared with the young adult rat group ($P < .05$), indicating that the old rats when subjected to anesthesia were more profoundly affected than young adult rats with regard to reductions in acetylcholine release and stress responses [35].

In another study, injecting atropine into rat brains, researchers were able to mimic a model for delirium in humans (defined by cortical electroencephalogram [EEG] recordings, maze performance, and observation of behaviors) [50]. Using this model, researchers were able to demonstrate higher EEG amplitudes and slower frequencies (hallmarks of drowsiness and sleep) in the atropine condition. Atropine-treated rats exhibited significant elevation in their mean maze time ($P < .016$, RM analysis of variance [repeated measures ANOVA]), and similarly to what is observed in delirious human subjects, atropine-treated rats exhibited difficulty with attention and memory, sleep-wake reversal, and changes in usual behavior.

Other animal studies have revealed impairment in cholinergic neurotransmission in models of encephalopathy/delirium, hypoxia, nitrite poisoning, thiamine deficiency, hepatic failure, carbon monoxide poisoning, and hypoglycemia [21,50,51]. Animal models have also demonstrated that immobilization may cause widespread ACh reduction [52,53]. This model may mimic the decreased mobility of critically ill patients.

Changes in ACh activity may be one of the mechanisms mediating the diffuse slowing pattern often described in the electroencephalogram (EEG) of patients suffering from delirium. The most common EEG finding is that of slowing of peak and average frequencies, decreased alpha activity, and increased theta and delta waves. Studies suggest that EEG changes correlate with the degree of cognitive deficit, but not with behavior assessed solely on degree of spontaneous movements. In other words, low levels of ACh do not slow the EEG to the point of sleep or absence of motor behavior, but seem to slow cognition [2,50,54–60].

Also with aging comes a broad decline in cardiovascular and respiratory reserves. Studies suggest that by age 85, vital capacity is reduced by nearly 40% and the arterio-alveolar gradient widens. Studies have demonstrated significant decreases in alveolar volume, nitric oxide and carbon monoxide lung transfer measurements, membrane diffusion, and capillary lung volume in relation to age ($P < .05$) and continuous negative pressure induced a significant increase in all variables [61]. Oxygen delivery to the brain may then be diminished at times of metabolic stress due to reduced capacity for compensatory changes in the arterial vasculature because of vasculopathy and senile changes. The normal aging process is accompanied by a complex series of changes in the autonomic control of the cardiovascular system, favoring heightened cardiac sympathetic tone with parasympathetic withdrawal and blunted cardiovagal baroreflex sensitivity. Together these changes have the potential to further magnify the effects of concomitant cardiovascular disease [62].

Animal studies have suggested that in patients with baseline organic cerebral disorders (eg, cerebrovascular disease) who are submitted to surgery, hypocapnia during anesthesia may cause tissue damage in the caudoputamen, which may be responsible for long-lasting postoperative delirium in patients with stroke and/or dementia [63].

Chronic forms of hypoperfusion may lead to subcortical ischemic vascular dementia, a relatively common form of dementia. This is more likely due to anatomic changes caused by aging in the arterial vascular system and predisposes the elderly to the effects of hypotension. Particular regions of the brain are more susceptible to ischemic hypoperfusive injury, including the periventricular white matter, basal ganglia, and hippocampus, leading to cognitive and memory problems. This may explain why older patients may be particularly sensitive to hypotension and hypoperfusion associated with orthostatic hypotension, congestive heart failure, or the changes associated with routine surgical procedures such as hip and knee replacement and coronary artery bypass graft (CABG) [64].

Similarly, increasing evidence supports the notion that chronic oxidative stress is the final pathway implicated in two major brain disorders characterized by cognitive impairment: cerebral chronic small vessel disease (microangiopathic leukoencephalopathy) and Alzheimer's disease (AD) [65]. Both disease processes seem to involve chronic hypoperfusion. The process of hypoperfusion appears to induce chronic oxidative damage in tissues and cells, largely due to the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These conditions outpace the capacity of endogenous redox systems to neutralize these toxic intermediates and may lead to a system imbalance or to a major compensatory adjustment to rebalance the system. This new redox state is generally referred to as ''oxidative stress'' and is associated with other age-related degenerative disorders, such as atherosclerosis, ischemia/reperfusion, and rheumatic disorders. Chronic ischemic injury can also affect differently selective areas of the brain [65] due to a well-documented variation in vulnerability of cerebral areas, with its imputability in spreading neuronal depression [66–68].

Medications and delirium

Factors associated with medication-induced delirium include the number of medications taken (generally more than 3) [69], the use of psychoactive medications [70], and the agent's anticholinergic potential [71]. There are a number of pharmacologic agents identified with an increased risk of developing delirium (Box 1). The number of agents used may be associated with pharmacokinetic or pharmacodynamic effects of the combined agents (eg, drug-drug interactions, metabolic inhibitions, additive negative effects). Similarly, studies have demonstrated a link between the use of pharmacologic agents with psychoactive effects and the occurrence of delirium in 15% to 75% of cases [15,72–77]. Certain agents with known psychoactive activity (ie, opiates, corticosteroids, benzodiazepines, nonsteroidal anti-inflammatory agents [NSAIDs], and chemotherapeutic agents) have been identified as major contributors to delirium in several studies [70]. Data suggest that a very high number of ventilated patients (more than 80%) develop delirium [6,7]. Similarly, about 90% of ventilated patients receive

Box 1. Risk of delirium with certain commonly used drugs

High risk
- Opioid analgesics
- Antiparkinsonian agents (particularly anticholinergic agents)
- Antidepressants (particularly anticholinergic agents)
- Benzodiazepines
- Centrally acting agents
- Corticosteroids
- Lithium

Medium risk
- Alpha-blockers
- Antiarrhythmics (lidocaine [lignocaine] has the highest risk)
- Antipsychotics (particularly sedating agents)
- β-Blockers
- Digoxin
- Nonsteroidal anti-inflammatory drugs
- Postganglionic sympathetic blockers

Low risk
- ACE inhibitors
- Antiasthmatics (highest risk with aminophylline and lowest risk with inhaled agents)
- Antibacterials
- Anticonvulsants
- Calcium channel antagonists
- Diuretics
- H_2-antagonists

Data from Bowen JD, Larson EB. Drug-induced cognitive impairment. Defining the problem and finding the solutions. Drugs Aging 1993;3(4):349–57.

benzodiazepines, opioids, or both to facilitate their management and ease the discomfort associated with intubation [78]. The question is, how are these two factors related?

The fact is, opioid agents have been implicated in the development of delirium [79–83] and are blamed for nearly 60% of the cases of delirium in patients with advanced cancer [84]. Narcotic use has been associated with the development of delirium [85–87]. Some have suggested that opioids cause delirium via an increased activity of dopamine (DA) and glutamate (GLU), while decreasing ACh activity [20]. The association of delirium with the use of meperidine has been well documented [30,64,88–91]. Meperidine is itself metabolized to normeperidine, a potent neurotoxic metabolite with marked anticholinergic potential [88]. Both its direct neurotoxic effect,

as well as the strong anticholinergic activity, may contribute to the development of delirium. Cases of opioid toxicity have been reported in relation to fentanyl and methadone [92–94].

Increasing evidence from experimental studies and clinical observations suggest that drugs with anticholinergic properties can cause physical and mental impairment. It has long been thought that low ACh levels may be associated with the disorientation, arousal, and cognitive problems observed in delirious patients [12]. Several studies have demonstrated a relationship between a drug's anticholinergic potential, as measured by SAA and the development of delirium [18,23,28,44,69,71,91,95–99]. Tune and colleagues [28,44,71,91,99,100] conducted several studies looking at the cumulative effect of drugs with subtle anticholinergic potential and their SAA (Box 2; Table 3).

A cross-sectional study [18] of 67 acutely ill older medical inpatients demonstrated that elevated SAA was independently associated with delirium. Furthermore, multivariate logistic regression revealed that the SAA quintile remained significantly associated with delirium, even after adjusted for ADL impairment, admission diagnosis of infection, and elevated white blood cell count. Among the subjects with delirium, a greater number of delirium symptoms were associated with higher SAA. Each increase in SAA quintile was associated with a 2.38-times increase in the likelihood of delirium (Fig. 2). Similarly, a study of elderly (ie, older than 80 years) ($n = 364$) patients demonstrated that the use of anticholinergic drugs is associated with impaired physical performance and functional status (Fig. 3) [101].

Studies have measured anticholinergic activity in blood and CSF from patients admitted for urological surgery and compared peripheral (ie, blood) and central (ie, CSF probes) anticholinergic levels [24]. Anticholinergic activity was determined by competitive radioreceptor binding assay for muscarinergic receptors and correlation analysis conducted for both sets of samples. The mean anticholinergic levels were 2.4 ± 1.7 in the patients' blood and 5.9 ± 2.1 pmol/mL of atropine equivalents in CSF, demonstrating that the anticholinergic activity in CSF was about 2.5-fold higher than in patients' blood. Still, there was a significant linear correlation between blood and CSF levels (Fig. 4). These studies have found that exposure to anticholinergic agents was an independent risk factor for the development of delirium, and specifically associated with a subsequent increase in delirium symptom severity.

Decreased cholinergic activity has been demonstrated in delirium and it is suggested that ACh repletion may serve as treatment of delirium [102]. In fact, physostigmine has been reported as reversing delirium when it was induced by anticholinergic agents in healthy volunteers [103], as well as delirium secondary to anticholinergic syndrome [104–108]. Conversely, studies in animals and healthy elderly adults have shown that cholinergic antagonist agents produced deficits in information processing, arousal, and attention and a reduced ability to focus [109,110].

Sleep pattern disruption and delirium

Sleep is a physiologic state that humans need to experience every day to restore physical and mental functions. Typically, humans adapt to a 24-hour circadian pattern, where they sleep at night and are awake during the day. This 24-hour internal clock (circadian pattern) is maintained by environmental factors, primarily light exposure, which affects melatonin secretion at night [111]. Conversely, sleep disruption may be another factor implicated as a mediating factor in the development of delirium, at least preponderantly in the ICU setting, if not in any hospitalized patient. Studies suggest that sleep deprivation may lead to the development of memory deficits [112–114]. Studies have shown that ''chronic partial sleep deprivation'' (ie, sleeping limited to 4 hours per night, for 5 consecutive nights) translates into cumulative impairment in attention, critical thinking, reaction time, and recall [115,116]. Furthermore, studies have found that sleep deprivation (even just 36-consecutive hours) may lead to symptoms of emotional imbalance (ie, short temper, mood swings, and excessive emotional response) likely due to a disconnect between the amygdala and the prefrontal cortex [117].

The above findings may contribute to many of the cognitive and behavioral changes observed in delirious patients. In fact, studies have demonstrated that sleep deprivation may lead to both psychosis [118] and delirium [51,119–121]. Mounting data suggest that cumulative sleep debt may not just be a cause of, but may aggravate or perpetuate delirium [122–127]. Using staff observations, there was a higher prevalence of delirium among sleep-deprived patients [128,129]. Overall, delirious patients were reported to have irregular patterns of melatonin release [130] and disrupted circadian rhythms, resulting in fragmented sleep/wake cycles and nighttime awakenings [131].

The amount of sleep debt associated to the critical care environment is not insignificant. Studies have found that the average ICU patient sleeps about 1 hour and 51 minutes per 24-hour period [132]. Factors associated with decreased length of sleep in the ICU include the high frequency of therapeutic interventions (eg, blood pressure monitoring, blood draws and flushing of lines, dressing changes and wound care), the nature of diagnostic procedures, pain, fear, and the noisy environment. As many as 61% of ICU patients report sleep deprivation, placing it among the most common stressors experienced during critical illness [133]. Previous studies used polysomnography (PSG) to demonstrate severe sleep fragmentation, a loss of circadian rhythm, and a decrease or absence of both slow-wave sleep and REM sleep in ICU patients [132,134,135]. In addition to causing emotional distress, sleep deprivation in the critically ill has been hypothesized to contribute to ICU delirium and neurocognitive dysfunction, prolongation of mechanical ventilation, and decreased immune function [136].

Melatonin secretion is one reflection of this internal sleep/wake mechanism. Melatonin levels are normally high during the night and low during daytime, being suppressed by bright light. Urinary excretion

Box 2. Medications with anticholinergic effects

Alprazolam
Amantadine
Amitriptyline
Ampicillin
Atropine
Azathioprine
Captopril
Cefamandole
Cefoxitin
Chlorazepate
Chlordiazepoxide
Chlorthalidone
Cimetidine
Clindamycin
Codeine
Corticosterone
Cycloserine
Cyclosporin
Desipramine
Dexamethasone
Diazepam
Digoxin
Diltiazem
Diphenhydramine
Dipyridamole
Dyazide
Flunitrazepam
Flurazepam
Furosemide
Gentamycin
Hydralazine
Hydrochlorathiazide
Hydrocortisone
Hydroxyzine
Imipramine
Isosorbide
Keflin
Lanoxin
Methyldopa
Nifedipine
Oxazepam

Oxybutynin chloride
Oxycodone
Pancuronium bromide
Phenelzine
Phenobarbitol
Piperacillin
Prednisolone
Ranitidine
Theophylline
Thioridazine
Ticrocillin
Tobramycin
Triamterene
Valproic acid
Vancomycin
Warfarin

Data from Tune LE, Egeli S. Acetylcholine and delirium. Dement Geriatr Cogn Disord 1999;10:342–4.

of 6-sulphatoxymelatonin (6-SMT)—the chief metabolite of melatonin—closely parallels serum melatonin concentrations. Therefore, the urinary excretion of 6-SMT can serve as a reliable measurement of serum melatonin. In a study of hospitalized, postoperative elderly patients, melatonin plasma samples were obtained every 2 hours from 19 patients without delirium and 10 with delirium after major abdominal surgery. Results demonstrated that patients without delirium showed nearly identical preoperative and postoperative melatonin secretion for 24 hours. On the other hand, patients with delirium experienced melatonin levels that were lower than preoperative values [137].

A study of medically hospitalized patients measured 6-SMT urinary levels twice: first in the acute phase of delirium (day when delirium rating scale [DRS] $\geq$ 14 points) and again after recovery (on the first day when DRS $\leq$ 6 points). The results demonstrated that among the hyperactive delirium patients, the levels of 6-SMT were lower during the acute delirium state than after recovery ($P < .001$). In contrast, among the hypoactive delirium patients, the levels of 6-SMT were higher during the acute delirium state than after recovery ($P < .01$). With the mixed patients, there was no difference in the level of 6-SMT between the two phases of delirium ($P < .45$) [138].

A study of blood and urine melatonin levels revealed an abolition of the circadian rhythm of physiologic melatonin release in deeply sedated ICU patients [139]. These findings suggest that the dyssynchronization of the melatonin secretion rhythm commonly found among critical care patients

Table 3
Anticholinergic drug used most frequently by the patients in the treatment and comparison groups

Drug	No. patients	Percentage of patients	Median (range) no. prescriptions[a] per patient	Median (range) day supply per prescription
Treated with donepzil				
Amitriptyline	18	4.3	2.0 (1–11)	30.0 (3–34)
Oxybutynin	15	3.6	5.0 (1–15)	30.0 (3–33)
Hyoscyamine	14	3.4	4.0 (1–11)	30.0 (10–30)
Diphenoxylate and atropine	12	2.9	1.0 (1–5)	5.0 (2–30)
Olanzapine	12	2.9	2.5 (1–13)	30.0 (4–30)
Hydroxyzine	11	2.6	4.0 (2–8)	30.0 (1–33)
Doxepin	11	2.6	6.0 (2–12)	30.0 (3–33)
Meclizine	9	2.2	2.0 (1–21)	8.0 (5–30)
Imipramine	7	1.7	6.0 (1–19)	30.0 (3–30)
Cyproheptadine	6	1.4	4.5 (1–11)	30.0 (2–30)
Not treated with donepzil				
Meclizine	16	3.8	1.0 (1–8)	12.0 (4–33)
Amitriptyline	14	3.4	4.5 (1–12)	30.0 (1–33)
Hyoscyamine	9	2.2	2.0 (1–11)	30.0 (1–30)
Oxybutynin	8	1.9	1.5 (1–5)	30.0 (8–33)
Hydroxyzine	8	1.9	2.0 (1–12)	30.0 (3–30)
Dicyclomine	7	1.7	2.0 (1–9)	30.0 (5–31)
Belladonna alkaloids and Phenobarbital	7	1.7	3.0 (1–11)	30.0 (2–30)
Phenylephrine/codeine/promethazine	4	1.0	1.0 (1–2)	5.0 (2–10)
Diphenoxylate and atropine	4	1.0	1.0 (1–1)	4.5 (3–6)
Orphenarine	4	1.0	3.0 (1–8)	30.0 (10–33)

[a] Prescriptions for large supplies of medication were converted to 30-day equivalents (eg, a prescription for a 90-day supply of medication was counted as three prescriptions, each with a 30-day supply).

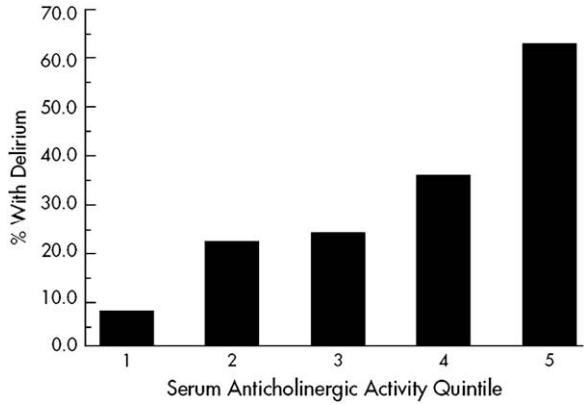

Fig. 2. Percentage of subjects with delirium by serum anticholinergic activity quintile. (*From* Flacker JM, Cummings V, Mach JR, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6(1):31–41; with permission.)

(possibly mediated or exacerbated by the use of sedative agents) may contribute to the development of delirium (Fig. 5). It also suggests that sedative agents may contribute to the development of delirium by more than one mechanism (ie, disruption of sleep patterns, central acetylcholine inhibition, disruption of melatonin circadian rhythm).

The immune system has long been regarded as a vulnerable target for sleep deprivation. Cytokines synthesized by the immune system may play a role in normal sleep regulation, by increasing non-REM sleep and decreasing REM sleep, and during inflammatory events, an increase in cytokine levels may intensify their effects on sleep regulation [140]. Current evidence suggests that acute and chronic sleep deprivation is associated with decreased proportions of natural killer cells [141], lower antibody titers following influenza virus immunization [142], reduced lymphokine-activated killer activity, and reduced interleukin (IL)-2 production [143]. Moreover, sleep deprivation may alter endocrine and metabolic functions, altering the normal pattern of cortisol release and contributing to alterations of ''glucocorticoid feedback regulation'' [144], glucose tolerance, and insulin resistance [145].

Trauma, surgery, systemic inflammation, and delirium

Delirium may represent a central nervous system (CNS) manifestation of a systemic disease state that has indeed crossed the blood brain barrier (BBB). Many of the circumstances associated with a high incidence of delirium (eg, infections, medication use, postoperative states) may be associated with BBB integrity compromise. As a response to traumatic events (including the trauma of surgery) the uniform cascade of interacting processes

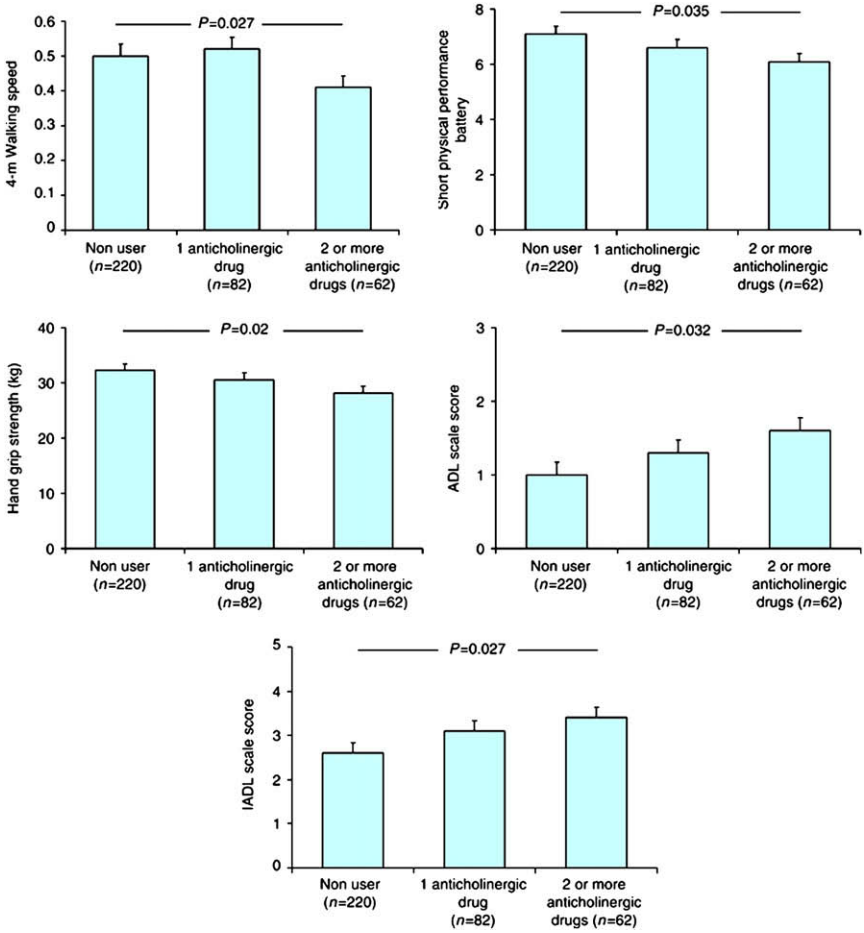

Fig. 3. Anticholinergic drugs and physical function among frail elderly population. (*From* Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 2007;81(2):235–41; with permission.)

known as the "systemic inflammatory response" is activated. Some surgical procedures may increase the risk of developing delirium, presumably because of the complexity of the surgical procedure, the extensive use and type of intraoperative anesthetic agents, and potential postoperative complications [146]. The more intense the primary insult is, the more pronounced is the inflammatory response. Illness processes and surgical procedures offer several triggering factors: use of anesthetic agents, extensive tissue trauma, elevated hormone levels, blood loss and anemia, blood transfusions, use of extracorporeal circulation, hypoxia, ischemia and reperfusion, formation of heparin–protamin complexes, microemboli formation and migration, and the inflammatory process. Similarly, studies have demonstrated that the

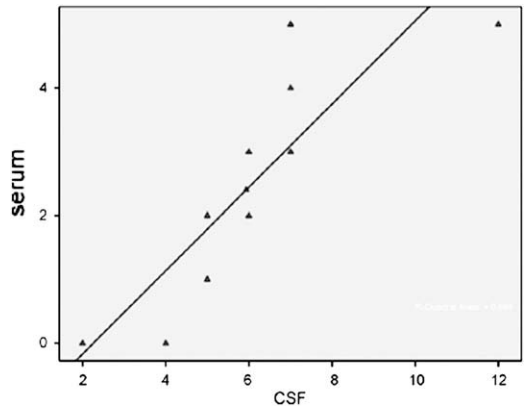

Fig. 4. Anticholinergic activity. Correlation analysis according to Pearson (r = 0,861; $P < .001$). The results are reported in pmol/mL of atropine equivalents. (*From* Plaschke K, et al. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. Neurosci Lett 2007;417(1):16–20; with permission.)

severity of the patient's initial injury or underlying medical problem (as measured by Acute Physiology and Chronic Health Evaluation [APACHE] scores) is significantly directly correlated with the development of delirium [14,30,147].

During or after illness processes or surgery, leukocytes adhere to endothelial cells (EC) and become activated. This leads to degranulation, which releases free oxygen radicals and enzymes, which in turn leads to EC membrane destruction, loosening of intercellular tights, extravascular fluid shift, and formation of perivascular edema, changes that are likely to occur within the brain tissue as well. Thus, systemic inflammation as a response to surgical trauma may cause diffuse microcirculatory impairment. The most relevant pathologies include leukocyte adhesion to vessel lining, endothelial cell swelling, perivascular edema, narrowing of capillary diameters, and lowered functional capillary density. These morphologic changes lead to a decrease of nutritive perfusion and to longer diffusion distance for oxygen. Because ACh synthesis is especially sensitive to low oxygen tension, decreased ACh availability and symptoms of its deficiency readily develop [148].

The magnitude of the inflammatory response after surgery or induced by medical illness has been implicated as a risk factor of neurocognitive decline, including delirium. This has been well documented after various surgical procedures [149–151]. Under normal conditions, the BBB inhibits cytokines and many medications from passing across capillaries into the brain parenchyma so the brain is relatively protected from the harmful effects of systemic inflammation [152]. Chemokines are locally acting cytokines that may enhance migration of inflammatory cells into the brain by

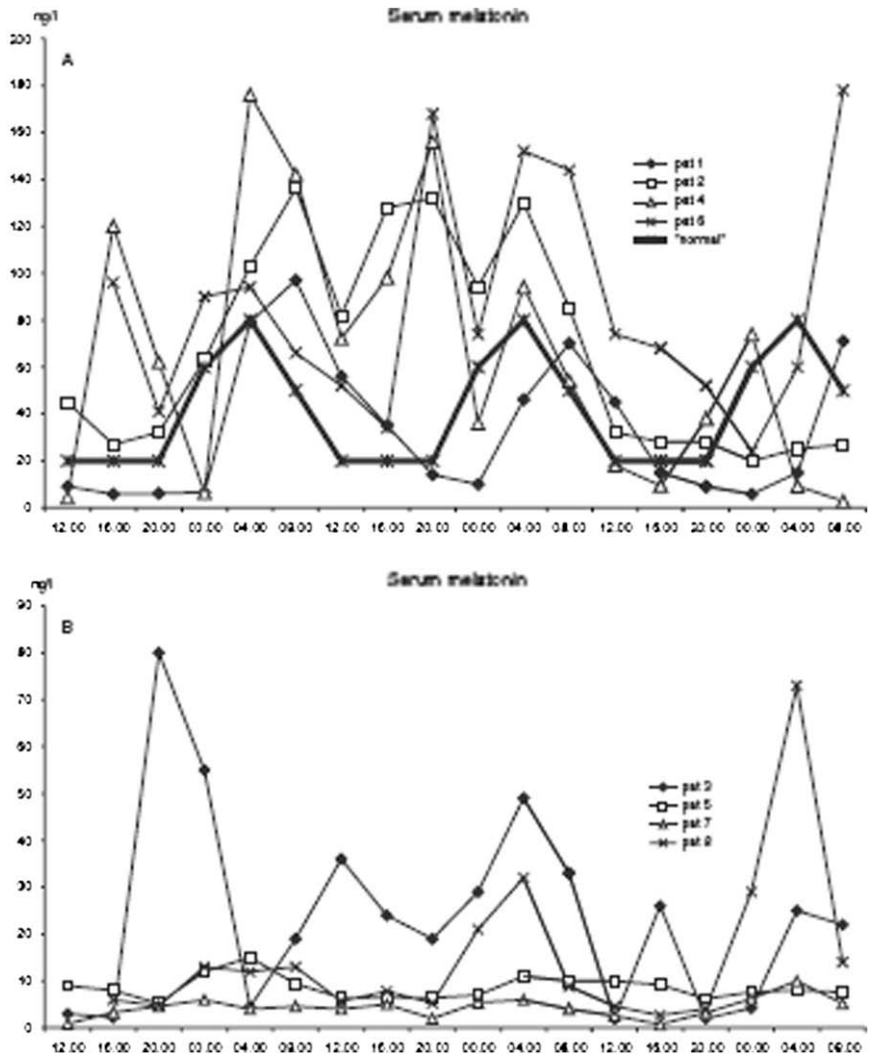

Fig. 5. Serum melatonin (ng/L) in eight critically ill subjects. The serum melatonin rhythm was found to be disturbed in all but one patient (*A*, *B*). The exception was patient 8. Her melatonin levels were low during her first day in the ICU, rising to much higher peak values on days 3 to 4. She began to recover a clear melatonin rhythm already on day 2, with a maximum at 4:00 AM. (*From* Olofsson K, Alling C, Lundberg D, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. Acta Anaesthesiol Scand 2004;48(6):679–84; with permission.)

compromising the BBB integrity [153–156]. Compromise of the BBB integrity allows the brain to become more susceptible to the effects of systemic inflammation [153,157]. Transient increases in the levels of circulating inflammatory markers (10 to 100 times more than baseline) has been

hypothesized to result from tissue damage, adrenal stress response, cardiopulmonary bypass, and/or anesthesia [158,159].

A study was conducted examining the expression patterns of pro- and anti-inflammatory cytokines in acutely medically ill, hospitalized elderly patients (ages $\geq$65; n = 185) with and without delirium [160]. Patients underwent cognitive and functional examination by validated measures of delirium, memory, and executive function, and measurements of C-reactive protein (CRP) and cytokines (IL-1beta, IL-6, tumor necrosis factor [TNF]-alpha, IL-8, and IL-10). A total of 34.6% of subjects developed delirium within 48 hours after admission. Compared with patients without delirium, delirious patients were older and had experienced more frequent preexistent cognitive impairment. In patients with delirium, significantly more IL-6 levels (53% versus 31%) and IL-8 levels (45% versus 22%) were above the detection limit as compared with patients who did not have delirium, even after adjusting for infection, age, and cognitive impairment. This suggests that pro-inflammatory cytokines may contribute to the pathogenesis of delirium.

In a similar study, acutely medically ill patients (n = 164), 70 years or older, were studied within 3 days of hospital admission and reassessed twice weekly until discharge, to identify and follow the clinical course of delirium [161]. Patients underwent measurements of apolipoprotein-E (APOE) genotype and the level of circulating cytokines. Researchers found that delirium was significantly ($P < .05$) associated with a previous history of dementia, age, illness severity, disability, and low levels of circulating insulin-like growth factor 1 (IGF-1). Recovery was significantly ($P < .05$) associated with lack of APOE 4 allele and higher initial interferon (IFN)-gamma. It further found a positive relationship between delirium with APOE genotype, IFN-gamma, and IGF-I, but not with IL-6, IL-1, TNF-alpha, and leukemia inhibitory factor.

In a cohort of elderly hip-fracture patients (n = 41), serum was obtained during the first 10 hours after fracture and before surgery, 48 to 60 hours postoperative, and 7 and 30 days postoperative, measuring CRP, IL-1beta, IL-6, IL-8, TNF-alpha, IL-10, and IL-1 receptor antagonist (IL-1RA) [162]. A significant increase was found postoperatively for CRP, IL-6, TNF-alpha, IL-1RA, IL-10, and IL-8. CRP kinetics curves were higher in patients with complications as a group, and in those suffering from infections, delirium, and cardiovascular complications. Additional complications appeared in patients with impaired mental status (IMS) versus cognitively intact patients. Analyzing the interaction effect of complications and IMS on CRP and cytokine production demonstrated that the increase in CRP was independently related to complications and IMS. IL-6, IL-8, and IL-10 were higher in IMS patients but not in patients with complications without IMS. This suggests that only CRP significantly and independently increases in patients who are mentally altered and in patients with complications, whereas cytokines significantly increase only in mentally altered patients.

Similarly, a study of cardiac surgery patients (n = 42) measured the serum concentrations of 28 inflammatory markers [163]. Inflammatory markers were assigned to five classes of cytokines, which are capable of disrupting BBB integrity in vitro. A class z score was calculated by averaging the standardized, normalized levels of the markers in each class. Beginning on postoperative day 2, patients underwent a daily delirium assessment. The study found that patients who went on to develop delirium had higher increases of chemokines compared with matched controls. Among the five classes of cytokines, there were no other significant differences between patients with or without delirium at either the 6-hour or postoperative day 4 assessments.

Several risk factors for delirium such as severe illness, surgery, and trauma can induce immune activation and a physical stress response comprising increased activity of the limbic-hypothalamic-pituitary-adrenocortical axis, the occurrence of a low T3 syndrome, and, possibly, changes in the permeability of the BBB [164].

Furthermore, some data suggest that inflammation may enhance the detrimental effects of hypoxia in cases of brain injury and long-term cognitive dysfunction. Using a porcine model, Fries and colleagues [165] found that acute lung injury/acute respiratory distress syndrome (ALI/ARDS) was associated with significantly greater hippocampal injury and higher serum levels of protein S100b, a marker of glial injury, than seen in animals that were exposed to hypoxemia alone without ALI/ARDS. These findings suggest that systemic inflammation linked to ALI/ARDS may have contributed to the brain injury seen in this model.

Cortisol, the hypothalamic-pituitary-adrenal axis, and delirium

Glucocorticoid hormones are important for coping with stress and have significant effects on the mobilization of energy substrates and inhibition of nonvital processes [166,167]. Yet, glucocorticoid hormones may have deleterious effects on mood and memory during prolonged excessive secretion. Some have suggested that glucocorticoids may be important for the pathogenesis of delirium, especially in later life [168,169]. In fact, delirium has been reported in cases of hypercortisolism associated with surgery [169], Cushing's syndrome [51], and dementia [170]. In demented patients, significant differences were found in basal cortisol levels between groups of patients with different severities of delirium. Patients without delirium had significantly lower basal cortisol levels than patients with mild delirium and these had significantly higher basal cortisol levels than patients with moderate/severe delirium. Significant differences in post–dexamethasone suppression test (DST) cortisol levels between patients with different degrees of delirium were also found, with the highest values in the moderate/severe delirium group. An increase in the frequency of nonsuppressors with increased severity of delirium was seen (Fig. 6) [170].

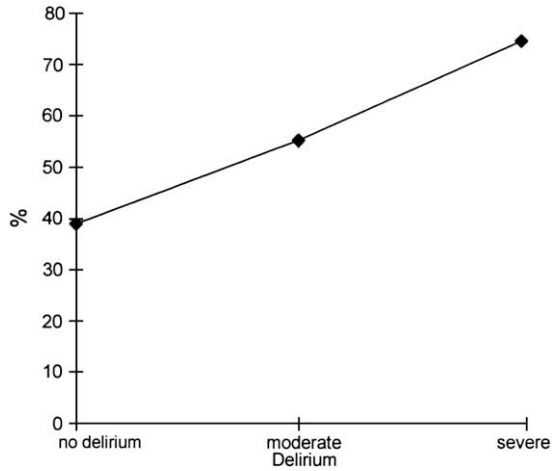

Fig. 6. Percentages of nonsupressors in delirium. A significant difference in the occurrence of nonsuppressors was found between patients with different severity of delirium ($P = .004$). An increase in the frequency of nonsuppressors with increased severity of delirium was seen: no delirium (n = 105) 33%, mild delirium (n = 47) 51%, and moderate/severe delirium (n = 20) 70%, respectively. (*From* Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. Int Clin Psychopharmacol 2001;16(1):39–47; with permission.)

Studies have found that, early after a stroke, delirium seems to be associated with an increased adrenocortical sensitivity to adrenocorticotropic hormone (ACTH) stimulation and a decrease in glucocorticoid-negative feedback [171], even after controlling for possible confounding factors, including the extent of functional impairment and age. Also, increased cortisol excretion after stroke is associated with disorientation [172].

A key abnormality related to cortisol excess in delirium seems to be abnormal ''shut-off'' of the hypothalamic-pituitary-adrenal (HPA) axis tested by the DST. In experimental models, the hippocampal formation is of prime importance for normal HPA axis shut-off. In this brain area, a close interaction between neurotransmitters, notably acetylcholine, serotonin, and noradrenaline, and glucocorticoid receptors, is relevant for the development of delirium in elderly patients with stroke and neurodegenerative brain diseases (Fig. 7) [173].

Steroid and thyroid hormones may act on nuclear gene transcription by activating protein receptors, which in turn bind to hormone response elements (HREs). Among these cell-specific processes regulated by steroid receptors is energy metabolism through increased synthesis of respiratory enzymes. As some of these enzymes are encoded by both nuclear and mitochondrial genes, coordination of their synthesis is probable, inter alia, at the transcriptional level. Some have demonstrated a direct effect of steroid hormones on mitochondrial gene transcription, suggesting that glucocorticoid

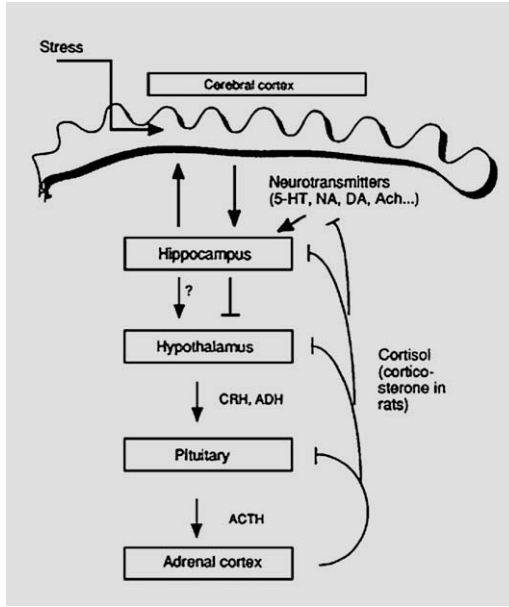

Fig. 7. Glucocorticoid-neurotransmitter interactions. Alterations in neurotransmitter input may influence glucocorticoid receptor expression in the brain, notably the hippocampus. A decrease in receptor expression may decrease feedback sensitivity inducing high circulating glucocorticoid levels, especially after stress. This may influence neurotransmitter synthesis and receptor expression and also adversely affect neuronal function, survival, and possibly the development of delirium. (*From* Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. Dement Geriatr Cogn Disord 1999;10(5):345–9; with permission.)

receptors (GR) rapidly translocate from the cytoplasm into mitochondria after administration of glucocorticoids. Similar results were obtained for thyroid hormone receptor (TR alpha) localization, import, and binding to TR elements.

Excessive glucocorticoid levels seem to induce a vulnerable state in neurons. The hippocampus is a major target for these effects with its dense concentration of GR. Glucocorticoid excess may thus exacerbate cell death induced by hypoxia/ischemia, hypoglycemia, and seizures. This can be related to numerous adverse effects including inhibition of glutamate reuptake in the synaptic cleft, inhibition of calcium efflux or sequestration, exacerbation of breakdown of cytoskeletal proteins including tau, increase in reactive oxygen species, decrease in activity of antioxidant enzymes, a reduction in release of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA), and decreased production of neurotrophins, notably brain derived neutrophic factor [30]. Finally, glucocorticoid excess may contribute to energy failure of neurons by inhibiting glucose transport into cells [173–176].

The increased cortisol availability associated with illness and trauma (eg, burns, surgery) or exogenous steroid administration may indeed be associated with disruption of hippocampal function [1]. This disruption of normal hippocampal activity will further disinhibit the release of cortisol, thus sustaining high levels of circulating cortisol. High levels of circulating cortisol may then be associated with mitochondrial dysfunction and apoptosis [177], which may lead to confusion and disturbance of attention and memory [178,179]. There is suspicion that an increase in circulating cortisol may also exacerbate the catecholamine disturbances observed in delirium. If this is true, it is possible that the stress response itself may contribute to the pathogenesis of delirium [1].

Thus, the hippocampal-adrenal circuit may contribute to the amplification of deliriogenic factors [1]. There is evidence that relatively early during the metabolic stress leading to delirium the hippocampus begins to malfunction [174,180]. This leads to some of the memory dysfunction and errors in information processing, leading to confabulation, commonly seen in delirious patients. The loss of normal inhibition of adrenal steroidogenesis results in continuous secretion of peak amounts of corticosteroids, leading to further mitochondrial dysfunction and apoptosis and further exacerbation of the catecholamine disturbances described above [181,182]. Glucocorticoids themselves can further potentiate ischemic neuronal injury in areas of high concentration (eg, hypothalamus), as well as in areas where corticosteroid receptors are low (eg, cerebral cortex).

Large neutral amino acids and delirium

Another hypothesis in the etiology of delirium is that changes in large neutral amino acids (LNAAs), which are precursors of several neurotransmitters that are involved in arousal, attention, and cognition, may play a role in delirium [183]. All LNAAs (isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine, and valine) enter the brain by using the same saturable carrier, in competition with each other. As the concentration of one LNAA increases, CNS entry of other LNAAs declines [184]. For example, brain concentrations of serotonin may increase if the relative blood concentration of tryptophan (TRP) increases. Alternatively, serotonin concentrations may decrease if other LNAA concentrations are increased relative to TRP. Phenylalanine (PHE) has the additional interesting property of possible conversion to neurotoxic metabolites and competes with TRP for entry into the brain and subsequent metabolism [185]. Several studies have demonstrated a relationship between elevated PHE/LNAA ratios and delirium.

A study of cardiac surgery patients ($n = 296$) found that elevations of the PHE/LNAA ratio were independently associated with postoperative delirium [186]. Other studies of patients with septic encephalopathy have also reported increased levels of PHE and PHE metabolites in the plasma and

CSF of those with encephalopathy [187,188]. Furthermore, elevated levels of PHE have been associated with prolonged performance time and impaired higher integrative function in older treated patients with phenylketonuria [189,190]. Finally, studies of elderly medically ill patients suggest that an elevated plasma PHE/LNAA ratio during acute febrile illness is associated with delirium (Fig. 8) [19,191].

Serotonin (5HT) is one of the neurotransmitters that may play an important role in medical and surgical delirium. Normal 5HT synthesis and release in the human brain is, among others, dependent on the availability of its precursor tryptophan (TRP). Both increased and decreased serotonergic activity have been associated with delirium. Hepatic encephalopathy has been associated with both elevated TRP availability and increased cerebral 5HT. Excess serotonergic brain activity has been related to the development of psychosis, as well as serotoninergic syndrome of which delirium is a main symptom. On the other hand, alcohol withdrawal delirium, delirium in levodopa-treated Parkinson patients, and postoperative delirium have been related to reduced cerebral TRP availability from plasma suggesting diminished serotonergic function. Sudden discontinuation of serotonin (5HT) reuptake inhibitors has been associated with a number of psychologic and neuropsychiatric syndromes, including delirium [192–194].

Hepatic dysfunction may lead to decreased metabolism of precursor amino acids (ie, phenylalanine, tyrosine, tryptophan), which leads to increases in availability of tryptophan, which leads to increases in 5HT. In fact, increased 5-hydroxyindoleacetic acid (5-HIAA) levels have been described in the CSF of subjects with hepatic encephalopathy and in patients suffering from hypoactive delirium [1,195–198]. On the contrary, some have

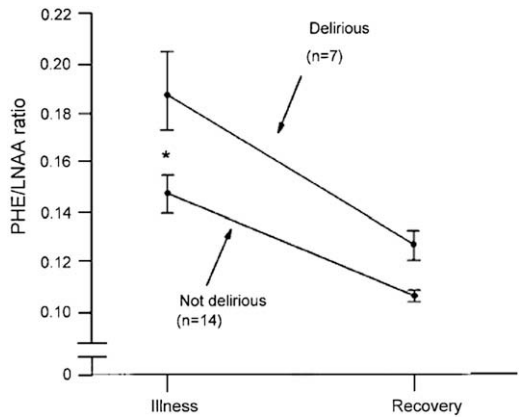

Fig. 8. PHE/LNAA ratio during illness and recovery in subjects with and without delirium. This figure demonstrates that delirious individuals had a significantly higher PHE/LNAA ratio during illness than nondelirious individuals ($P = .03$). (*From* Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. J Gerontol A Biol Sci Med Sci 2000;55(5):B249–52; discussion B253–4; with permission.)

suggested that low 5HT levels, as it occurs in hypoxia, may be associated with hyperactive delirium [199–201].

Oxidative failure due to hypoxia, anemia, hypoperfusion, or ischemia and neurotransmitter imbalances

Severe illness processes, combined with both decreased oxygen supply and/or increased oxygen demand may lead to the same common end problem, namely decreased oxygen availability to cerebral tissue. Patients in the critical care setting are particularly at risk to suffer the effects of hypoperfusion, hypoxemia, and hypoxia. There may be extrinsic factors leading to decreased oxygen exchange, such as pump failure with mild global cerebral oligemia (eg, cardiac disease, intraoperative hypotension), intrinsic lung disease (eg, pulmonary edema, pneumonia, acute respiratory failure [ARF], acquired respiratory distress syndrome [ARDS]), and anemia (eg, failure to transport a sufficient amount of O_2). There may also be sources of increased O_2 demand in medically ill individuals, including but not limited to hyperthermia (eg, an increase in O_2 consumption as represented by a rise in oxygen consumption (VO_2) by 10% to 13% for every degree centigrade in body temperature [202]), seizures, burns, hyperthyroidism, myocardial infarction, septic shock, multiorgan failure, and trauma, including the trauma of surgery [203–206].

The work of Rossen and colleagues in 1943 [207] and later Corel and colleagues in 1956 [208,209] laid the foundation of our understanding of neuronal activity and its crucial dependence on the availability of substrates for aerobic metabolism. Animal studies suggest that many factors influence the hypoxic response: environmental conditions (eg, temperature, PaO_2 also affected by atmospheric pressure), comorbidities (eg, age, general health status), patterns of the hypoxic insult (ie, continuous versus intermittent), and finally duration (ie, chronic versus acute) of the hypoxic event. In response to hypoxia, diverse reconfigurations of widespread neuronal network seem to occur. A remodeling is accomplished at all levels of the nervous system (ie, molecular, cellular, synaptic, neuronal, network): synaptic transmission is depressed through presynaptic mechanisms and excitatory/inhibitory alterations involving potassium (K^+), sodium (Na^+), and calcium (Ca^{2+}) channels [210]. More recently, Harukuni and Bhardwaj [211] revisited the process by which cerebral ischemia leads to a rapid depletion of energy stores triggering a complex cascade of cellular events, including cellular depolarization and Ca^{2+} influx, resulting in excitotoxic cell death (Fig. 9).

Inadequate oxidative metabolism may be one of the causes of the problems observed in delirium, namely, inability to maintain ionic gradients causing ''spreading depression'' [200,212–216]; abnormal neurotransmitter synthesis, metabolism, and release [217–225]; and a failure to effectively eliminate neurotoxic by-products (also, see Fig. 1) [218,219,223].

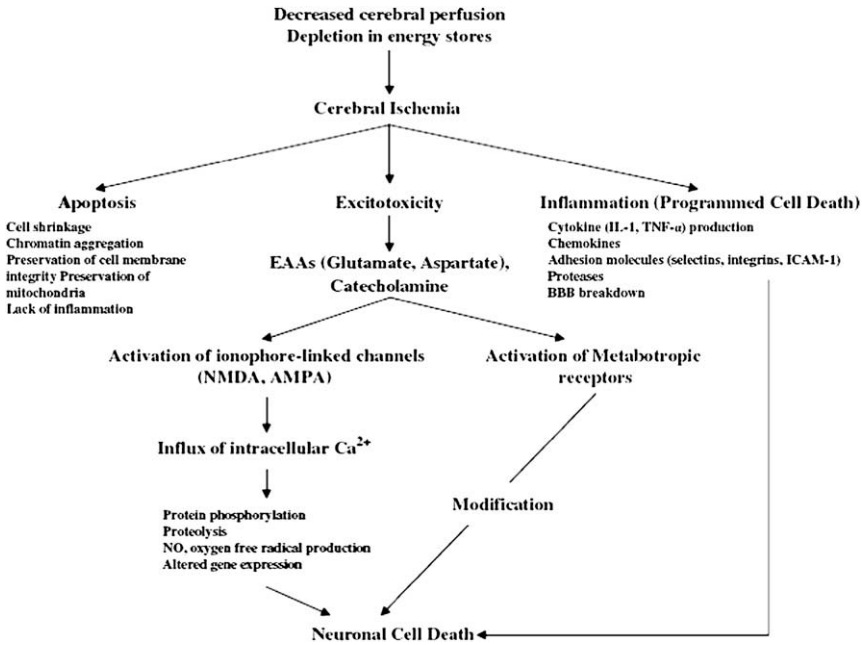

Fig. 9. Mechanisms of brain injury after global cerebral ischemia. (*From* Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin 2006;24:1–21; with permission.)

Indeed, decreased oxygenation causes a failure in oxidative metabolism, which leads to a failure of the ATP-ase pump system [226]. When the pump fails, the ionic gradients cannot be maintained, leading to significant influxes of Na^+ followed by Ca^{2+}, while K^+ moves out of the cell [226,227]. Some have theorized that it is the excess inward flux of Ca^{2+} that precipitates the most significant neurobehavioral disturbances observed in delirious patients [228,229]. The influx of Ca^{2+} during hypoxic conditions is associated with the dramatic release of several neurotransmitters, particularly GLU and dopamine (DA). GLU further potentiates its own release as GLU stimulates the influx of Ca^{2+} [228–230], and it accumulates in the extracellular space as its reuptake and metabolism in glial cells is impeded by the ATPase pump failure [226]. In addition, at least two factors facilitate dramatic increases in DA: first, the conversion of DA to norepinephrine (NE), which is oxygen dependent, is significantly decreased; second, the catechol-o-methyl transferase (COMT) enzymes, required for degradation of DA, get inhibited by toxic metabolites under hypoxic conditions, leading to even more amassment of DA [231]. At the same time, serotonin (5HT) levels fall moderately in the cortex, increase in the striatum, and remain stable in the brainstem (BS) [195].

Hypoxia also leads to a reduced synthesis and release of ACh, especially in the basal forebrain cholinergic centers [17]. Indeed, cholinergic neurotransmission is particularly sensitive to metabolic insults, such as diminished availability of glucose and oxygen [21]. The reason is simply that ACh synthesis requires acetyl coenzyme A, which is a key intermediate linking the glycolytic pathway and the citric acid cycle. Thus, reduction in cerebral oxygen and glucose supply and deficiencies in enzyme cofactors such as thiamine may induce delirium by impairing ACh production [232–234].

There are definite data correlating poor oxygenation and cerebral dysfunction.

For instance, some have demonstrated that delirium can be induced in healthy control subjects by dropping PaO_2 to 35 mm Hg [33]. During cardiac arrest, there is total loss of oxygen input. From the pioneer work of Siesjo in 1978 [235], we know that once anoxia sets in, a neuron has about 12 seconds of remaining metabolic rate using its ATP, followed by 20 seconds from the ATP-reserve phosphocreatine (PCr). In the delirious critically ill patient, the problem is not total loss of oxygen input, but more a possible imbalance in supply and demand, still leading to chronic hypoxic injury. A recent prospective study of patients ($n = 101$) admitted to the ICU examined whether oxidative metabolic stress existed within the 48 hours before delirium onset. As expected, older patients experienced a higher incidence of delirium. The results further demonstrated that three measures of oxygenation (ie, hemoglobin level, hematocrit, pulse oximetry) were worse in the patients who later developed delirium. Similarly, clinical factors associated with greater oxidative stress (eg, sepsis, pneumonia) occurred more frequently among those diagnosed with delirium [236].

Studies have demonstrated a strong correlation between mental function on postoperative days (POD) 3 and 7, and the O_2 saturation on POD 0 [237]. Clinically significant cognitive impairment has been observed in patients suffering from obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) [238]. The severity of these deficits is inversely correlated with arterial oxygenation [239]. In thoracotomized patients, there is a correlation between postoperative O_2 saturations and delirium. Studies have shown that decreased postoperative O_2 saturations are associated with the development of delirium, with delirium reversal after O_2 supplementation [240]. Finally, septic patients suffer from both increased oxygen demand and decreased oxygen delivery as they are proven to have lower hemoglobin level, lower cerebral blood flow, and lower cerebral O_2 delivery compared with controls [241].

Animal studies suggest that neuronal susceptibility to ischemic injury is not uniform: particularly vulnerable are the CA1 and CA4 regions of the hippocampus, the middle laminae of the neocortex, the reticular nucleus of the thalamus, the amygdala, the cerebellar vermis, select neurons in the caudate nucleus, and certain brain stem nuclei, such as the pars reticulata of the substantia nigra [242]. This sensitivity appears to be caused by the

inherent properties of neurons in those brain regions, and not by uneven circulation. Hypotheses for the differential susceptibilities of certain brain regions to ischemia include the induction of certain enzyme systems such as heat shock proteins, or c-fos or c-jun gene products, which confer a relative sensitivity to ischemia, and nonuniform cellular energy requirements (eg, small surface neurons require less, or oxidative-enzymes-dependent circuitries) [243]. Indeed, the more membrane that a neuron has, the more ATP must be dedicated to ion pumps. Conversely, the less cytoplasm a neuron has, the fewer mitochondria will be available to supply ATP. Therefore, the SAVR (surface area to volume ratio) of a neuron helps to define how resistant a neuron may be to oxidative stress.

The basal ganglia, thalamus, Purkinje, layer 3 of the cortex, and the pyramidal neurons of the hippocampus are particularly vulnerable to hypoxia, but the degree of damage may vary depending on the etiology [244–247]. Overall, the least susceptible neurons to oxidative stress are the small inhibitory interneurons (ie, GABAergic, glycinergic), while the most susceptible neurons are those of the ACh, DA, histamine (HA), NE, and 5HT pathways [68]. This constitutes another robust argument substantiating the neurotransmitter imbalances theories in delirium due to oxidative failure.

Besides hypoxia, a superimposed global mild ischemic injury (ie, global oligemic injury) is often present in critically ill patients galvanizing the oxidative failure. Indeed, patients in the critical care setting are particularly at risk to suffer the effects of hypoperfusion resulting from a number of potentially controllable extrinsic factors (eg, intraoperative hypotension, cardiac failure, hypotensive anesthetic agents, diuretics, and blood pressure lowering agents).

Hypoxia, anemia, and hypoperfusion with global cerebral mild ischemia (ie, oligemia) are all common factors leading to neurotransmitter imbalances that have a well documented structural spreading to susceptible neurons in a specific order. This ''spreading depression'' correlates clinically with the symptoms and signs of progressing deliria [66,67,216], and makes another robust argument substantiating this coherent etiologic theory on delirium mechanisms.

The role of dopamine

Elevations of DA have long been associated with the development of delirium [19,26,248,249]. There are several additional metabolic pathways that lead to significant increases in DA under impaired oxidative conditions: first, significant amounts of DA are released and there is a failure of adequate DA reuptake. At the same time the influx of Ca^{2+} stimulates the activity of tyrosine hydroxylase (TH) [250], which converts tyrosine to 3,4-dihydroxyphenylalanine (DOPA), thus leading to increased DA production and further uncouples oxidative phosphorylation in brain mitochondria [227]. The outcome is further disruption of adenosine triphospate (ATP) production. Decreased ATP and the increased production of toxic metabolites of DA

(formed under hypoxic conditions) inhibit the activity of the oxygen-dependent catechol-O-methyl transferase (COMT) [37,231], which is the major extracellular deactivator of DA, further leading to high levels of DA. Furthermore, an increase in the firing rates of catecholamine neurons may further induce TH synthesis, which leads to even more DA production [251].

The influx of Ca^{2+} also stimulates DA release, anoxic depolarization [252], and the activation of catabolic enzymes [229]. This is another mechanism by which impaired oxidative conditions leads to the breakdown in ATP-dependent transporters, which in turn leads to a decrease in DA reuptake [253–255]. The increases in DA can be considerable. In fact, levels as high as 500-fold increase in extracellular DA concentrations have been recorded in cases of striatal ischemia [195,198,220,221,256]. Of note, the excess in extracellular DA can in itself promote more Ca^{2+} influx, further perpetuating the problem [220]. The failure to adequately limit the production of and effectively eliminate toxic DA metabolites is a source of ongoing cellular injury during hypoxia and may contribute to some of the features of a post-delirium syndrome [1]. Figiel and colleagues [257] also found an excess of DA in association with delirium induced by electroconvulsive therapy. Similarly, studies show that DA agonists can create slower EEG in spite of motor hyperactivity [258], which represents a perfect symptomatological match to hyperactive delirium.

The dramatic increases in DA availability may lead to some of the neurobehavioral alterations observed in delirious patients—primarily the signs of hyperactive or mixed type delirium, namely increased psychomotor activity, hyperalertness, agitation, irritability, restlessness, combativeness, distractibility, and psychosis (ie, delusions and hallucinations) (see Fig. 1) [256,259,260]. In addition to generation of H_2O_2 and quinone formation, L-Dopa- and DA-induced cell death may result from induction of apoptosis, as evidenced by increases in caspase-3 activity. Also, DA per se induces apoptosis by a mechanism independent of oxidative stress [261].

Interestingly, depletion in DA by alphamethylparatyrosine actually protects neurons against hypoxic stress and injury [262,263]. Similarly, DA blockade can be used to reduce hypoxic damage in the hippocampus [264].

Hepatic dysfunction and the role of glutamate in delirium

DA may exert its deliriogenic activity by more than one mechanism. The direct activity of DA can be observed in cases of toxicity with substances known to increase DA release of availability, such as amphetamines, cocaine, and dopamine. On the other hand, DA may have a secondary activity by enhancing GLU-mediated injury.

Thus, increased GLU availability may be due to the influx of Ca^{2+} caused by a number of factors (eg, hypoxia, excess DA) best known of all is liver failure. Hepatic failure leads to hyperammonemia, which in turn leads to excessive N-methyl-D-aspartate (NMDA) receptor activation. This leads to dysfunction of the glutamate-nitric oxide-cGMP (cyclic

guanosine monophosphate) pathway, which leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy.

As described above, the influx of Ca^{2+} during hypoxic conditions is associated with the release of several neurotransmitters, particularly high levels of GLU [229,230,265,266]. Hypoxic conditions may further extend GLU activity as the absence of extracellular mechanism of degradation require the functioning of ATP-dependent reuptake, which is impaired under these conditions [226]. GLU is an excitatory neurotransmitter that may lead to neuronal injury via its activation of NMDA receptors [267–271]. Nevertheless, it appears that GLU requires the presence of DA to exert some of its toxic effects, namely its Ca^{2+}-induced neuronal injury [219,221,223,228]. At high levels, DA may cause enough depolarization of neurons as to activate the voltage-dependent NMDA receptor, therefore facilitating the excitatory effect of GLU (see Fig. 1) [272].

At least in one study of high-risk adults (n =557) undergoing cardiac surgery, serum concentrations of NMDA receptor antibodies, as measured by serum concentrations of (NMDA) receptor antibodies (NR2Ab) were predictive of severe neurologic adverse events (eg, delirium, transient ischemic attack, or stroke). Patients with a positive NR2Ab test ($\geq$2.0 ng/mL) preoperatively were nearly 18 times more likely to experience a postoperative neurologic event than patients with a negative test ($<$2.0 ng/mL) (Fig. 10) [273].

Glutamate (the principal excitatory neurotransmitter) is metabolized by glutamate decarboxylase (GAD) (using pyridoxal phosphate or vitamin B6, as a cofactor) into GABA (the principal inhibitory neurotransmitter).

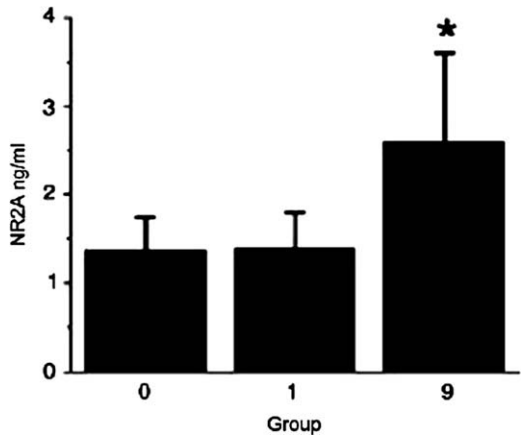

Fig. 10. Preoperative serum NR2Ab and postoperative neurologic events. The 0 indicates no neurologic event; 1, anxiety or agitation; 9, confusion/delirium, transient ischemic attack, or stroke. Patients in group 9 had significantly higher preoperative serum NR2Ab than groups 0 or 1 ($P = 0.0004$). (*From* Bokesch PM, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. Stroke 2006;37(6):1432–36; with permission.)

GABA has also been implicated in the development of the delirium [274]. There is evidence to suggest that GABA activity is increased in delirium related to hepatic encephalopathy, but decreased in delirium caused by hypnotic or sedative withdrawal [275]. The precise role of GABA in hepatic encephalopathy is unclear, but at least one source found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276]. Reduced GABA has also been implicated in delirium that results from ethanol or CNS-depressant (eg, benzodiazepines, propofol, barbiturates) withdrawal.

Excessive activation of NMDA receptors leads to neuronal degeneration and cell death. Hyperammonemia and liver failure alter the function of NMDA receptors and of some associated signal transduction pathways. Acute intoxication with large doses of ammonia (and probably acute liver failure) leads to excessive NMDA receptor activation, which is responsible for ammonia-induced death. The function of the glutamate-nitric oxide-cGMP pathway is impaired in brain in vivo in animal models of chronic liver failure or hyperammonemia and in homogenates from brains of patients who died in hepatic encephalopathy. The impairment of this pathway leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy. Learning ability is reduced in animal models of chronic liver failure and hyperammonemia [277].

Hepatic dysfunction also is associated with an increase in unesterified plasma fatty acids, which leads to increased tryptophan levels, which leads to impairment in the active transport of homovanillic acid (HVA) through the BBB and out of the CSF [198]. In fact, in cases of hepatic failure, the above may lead to significant increases in CSF-HVA levels, despite initial normal DA levels. Eventually, this contributes to the excessive DA levels described above.

Finally, there is evidence that hepatic failure may be associated with a shift in the regional cerebral blood flow (rCBF) patterns and cerebral metabolic rates from cortical to more subcortical areas of the brain [278–283]. In fact, studies of end-stage liver disease using single-photon emission computed tomography (SPECT) brain scans demonstrated that their rCBF was decreased in bilateral frontotemporal and right basal ganglia regions as compared with control subjects and that impairment in cognitive tests was correlated with ratios of rCBF values [284].

Gamma-aminobutyric acid activity, central nervous system–depressant abuse, withdrawal states, and delirium

GABA has also been implicated in the development of the delirious state [274,285]. The role of GABA in hepatic encephalopathy and delirium is unclear, but at least one source found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276,286]. GABA activity has been found to be increased in delirium related

to hepatic encephalopathy and decreased in hypnotic/sedative withdrawal [275,287–290]. Reversely, reduced GABA serum levels are found in alcohol withdrawal [291] and antibiotic-induced delirium [292]. GABA is formed by the decarboxylation of glutamate by GAD. It is of note that GAD requires B6 (pyridoxine as a cofactor), and B6 has already been implicated as a prominent player in the development of delirium [20].

Oversedation has been found to be an independent predictor of prolonged mechanical ventilation. In a prospective, controlled study (n = 128) of adults undergoing mechanical ventilation, subjects were randomized to either continuous sedation or daily awakenings [293]. They found that the median duration of mechanical ventilation was 4.9 days in the intervention group (ie, daily awakening), as compared with 7.3 days in the control group ($P = .004$) (Fig. 11A), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P = .02$) (Fig. 11B).

Among the agents known to cause delirium and other cognitive impairments in the medically ill patient, GABAergic medications have been shown to be some of the most significant and frequent culprits [6,89,103,294–297]. There are several mechanisms by which sedative agents (eg, benzodiazepines, propofol) contribute to delirium: (1) interfering with physiologic sleep patterns (ie, significantly reduce slow-wave and REM sleep, increase spindles, increase cortical activity at low doses, and decrease EEG amplitude) [298–300]; (2) causing a centrally mediated acetylcholine deficient state (ie, interruption of central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus) [103,296,297]; (3) enhancing NMDA-induced neuronal damage [301]; (4) disrupting the circadian rhythm of melatonin release [139]; (5) disruption of thalamic gating function (ie, the ability of the thalamus to act as a filter, allowing only relevant information to travel to the cortex) leading to sensory overload and hyper-arousal [248]. Studies have demonstrated a direct the relationship between benzodiazepine use and the development of delirium [89]. In both Surgical-ICU and Trauma-ICU the use of benzodiazepines has been identified as an independent risk factor for the development of delirium [126]. In fact, studies have demonstrated that lorazepam is an independent risk factor for daily transition to delirium (Fig. 12) [30].

Alcohol and CNS-depressant substances cause intoxication through effects on diverse ion channels and neurotransmitter receptors, including $GABA_A$ receptors—particularly those containing δ subunits that are localized extrasynaptically and mediate tonic inhibition—and NMDA receptors. Alcohol dependence results from compensatory changes during prolonged alcohol exposure, including internalization of $GABA_A$ receptors, which allows adaptation to these effects. The short-term effects of alcohol result from its actions on ligand-gated and voltage-gated ion channels [302,303]. Prolonged alcohol consumption leads to the development of tolerance and physical dependence, which may result from compensatory functional

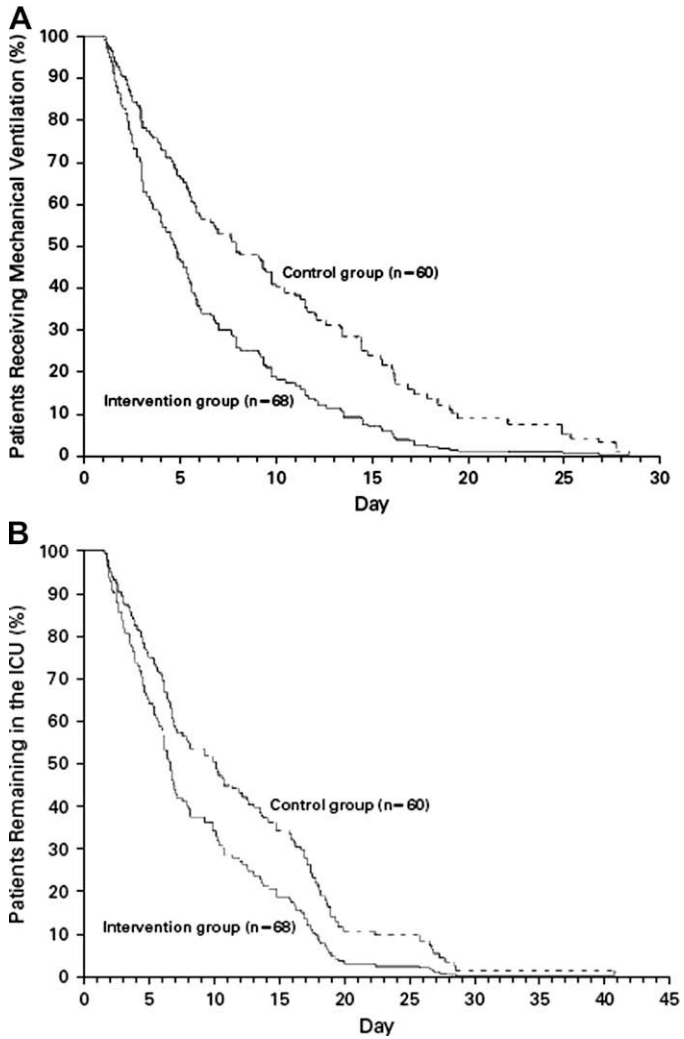

Fig. 11. (*A*) Analysis of the duration of mechanical ventilation, according to study group. After adjustment for base-line variables (age, sex, weight, APACHE II score, and type of respiratory failure), mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk of extubation, 1.9; 95% confidence interval, 1.3 to 2.7; $P < .001$). (*B*) Analysis of the length of stay in the intensive care unit (ICU), according to study group. After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), discharge from the ICU occurred earlier in the intervention group than in the control group (relative risk of discharge, 1.6; 95% confidence interval, 1.1 to 2.3; $P = .02$). (*From* Kress JP, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20):1471–77; with permission. Copyright © 2000, Massachusetts Medical Society.)

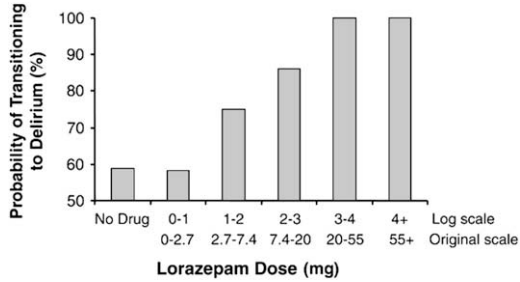

Fig. 12. Lorazepam and the probability of transitioning to delirium. Lorazepam and the probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered during the previous 24 hours. This incremental risk was large at low doses and plateaued at approximately 20 mg/d. (*From* Girard, et al. Delirium in the intensive care unit. Critical Care 2008;12(Suppl 3):S3; with permission; and *Adapted from* Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21–6; with permission.)

changes in the same ion channels. Similarly, acute administration of alcohol is known to stimulate 5-HT turnover, while chronic alcohol intake is reported to decrease 5-HT synthesis and release [304]. Not surprisingly, plasma noradrenergic (NA) levels [305] and 5-HT function [306] have been found to be elevated in alcoholic patients.

Ethanol modifies the functional activity of many receptors and ion channels, including NMDA [307,308], kainate [309], serotonin 5-HT3 [310], $GABA_A$ [311], and glycine [312] receptors as well as G protein–coupled inwardly rectifying potassium channels [313] and calcium channels [314]. $GABA_A$ receptors containing the δ subunit, in particular $\alpha4\beta2\delta$ and $\alpha6\beta2\delta$ receptors, are exceptionally sensitive to ethanol. Brain regions that express δ subunits, including the cerebellum, cortical areas, thalamic relay nuclei, and brainstem, are among those that are recognized to mediate the intoxicating effects of alcohol [315]. The mechanisms of alcohol dependence are less well understood than are those responsible for acute intoxication. However, it now appears that compensatory adaptation of $GABA_A$ receptors to prolonged ethanol exposure plays a critical role in alcohol dependence. Among the possible adaptive mechanisms, down-regulation of $GABA_A$ receptors, as a result of decreases in the surface expression of $\alpha1$ or $\gamma2$ subunits, is emerging as an important candidate [316].

Compensatory up-regulation of NMDA and kainate receptors as well as Ca^{2+} channels follow, leading to Ca^{2+} influx and changes associated with delirium [317]; these mechanisms may also have been implicated in alcohol dependence and withdrawal seizures. For example, the inhibitory effects of ethanol on NMDA receptors leads to up-regulation in the number of NMDA receptors in many brain regions, which may be an additional factor in the susceptibility to alcohol withdrawal seizures [318–320]. The relevance

of this mechanism is highlighted by the fact that NMDA-receptor antagonists are highly effective anticonvulsants in animal models of alcohol withdrawal seizures [321].

Alcohol withdrawal is associated with reduced density of synaptic $GABA_A$ receptors as well as alterations in $GABA_A$-receptor subunit composition that lead to reduced inhibitory efficacy; both effects would be expected to predispose to seizures. Indeed, susceptibility to alcohol withdrawal seizures has been associated with a loss of $GABA_A$-mediated inhibition [322]. Alcohol withdrawal has been linked to increased metabolism and release of NA/NE (noradrenaline or norepinephrine) [323,324], reduced α2 adrenoceptor function [325,326], reduced 5-HT function [327], and alterations in neuroendocrine responsivity to challenge with NA and 5-HT agents [328]. Withdrawal seizures are believed to reflect unmasking of these changes and may also involve specific withdrawal-induced cellular events, such as rapid increases in α4 subunit–containing $GABA_A$ receptors that confer reduced inhibitory function [316].

The role of histamine and delirium

Histamine receptors A1 (HA1) and A2 (HA2) are known to affect the polarity of cortical and hippocampal neurons [329,330] and pharmacologic antagonism of either receptors is sufficient to cause delirium [331]. Others have suggested that, during surgical stress and hypoxia, there may be an excessive release of HA, which may lead to delirium [332]. In these cases, blockade of either HA1 or HA2 receptors helped to limit neuronal death within the hippocampus [333,334]. So, both excess and deficiency of HA may be associated with delirium. Clinical experience has demonstrated that drugs like diphenhydramine, both anti-HA and anti-ACh, can cause delirium. Similarly, it has been reported that H2 blockers such as cimetidine and ranitidine may cause cognitive dysfunction and delirium in the elderly [1].

The role of somatostatin and endorphines in delirium

There is not a lot of data regarding somatostatin and delirium. Nevertheless, the available data on elderly delirious patients suggests that delirious patients showed significant reduction of somatostatin-like immunoreactivity (SLI) in CSF, as compared with the controls. Koponen and colleagues [335,336] also found a significant correlation between SLI levels and Mini-Mental State Examination scores. Koponen and colleagues [335,336] suggest a role for somatostatinergic dysfunction in the genesis of some symptoms of delirium, and postulate that somatostatinergic dysfunction may be linked to the long-term prognosis of delirious patients [335,336].

Other studies have demonstrated significant reductions in the β-endorphin-like immunoreactivity (BLI) values in the CSF of delirious patients ($n = 69$) compared with controls ($n = 8$). The changes in BLI had no

correlation with age or neuroleptic drug dosage, but did have a significant positive correlation with cognitive functioning as evaluated by the Mini-Mental State exam [337,338].

Electrolyte abnormalities, dehydration, and delirium

Dehydration is a reliable predictor of impaired cognitive status and delirium [15,339–341]. Objective data, using tests of cortical function, support the deterioration of mental performance in mildly dehydrated younger adults, and it would be expected the effects would be more profound in the elderly and medically ill [342]. Available evidence indicates the increased susceptibility of older adults to dehydration and the resulting complications, including delirium [343,344]. Dehydration in older adults has been shown to be a reliable predictor of increasing frailty, progressive deterioration in cognitive function, and an increased incidence in the development of delirium [340,345–349]. Studies have demonstrated a significant correlation between cognitive dysfunction and severity of dehydration, induced by a combination of fluid restriction and heat stress [350]. Subjects exhibited progressive impairment in mathematical ability, short-term memory, and visuomotor function once 2% body fluid deficit was achieved. Similarly, other studies have demonstrated impaired long-term memory following dehydration resulting from heat stress [351]. Animal studies have identified neuronal mitochondrial damage and glutamate hypertransmission in dehydrated rats. Additional studies have identified an increase in cerebral nicotinamide adenine dinucleotide phosphate-diaphorase activity (nitric oxide synthase, NOS) with dehydration. Available evidence also implicates NOS as a neurotransmitter in long-term potentiation, rendering this a critical enzyme in facilitating learning and memory. With aging, a reduction of NOS activity has been identified in the cortex and striatum of rats. The reduction of NOS activity that occurs with aging may blunt the rise that occurs with dehydration, and possibly interfere with memory processing and cognitive function [342]. Dehydration has been shown to be a reliable predictor of increasing frailty, deteriorating mental performance, and poor quality of life. In other words, dehydration may begin a cascade of events that lead to cognitive dysfunction and delirium.

There are four main pathways by which dehydration may cause cognitive dysfunction and delirium (Fig. 13) [342]: (1) dehydration may cause intracellular changes leading to increased cytokine concentrations, increased anticholinergic burden, and altered pharmacokinetics; (2) dehydration leads to intravascular volume depletion, causing cerebral hypoperfusion, thromboembolic disorders, and cardiac ischemia; (3) dehydration causes extravascular changes, leading to water and electrolyte imbalances, contraction alkalosis, and uremia secondary to acute renal failure; and (4) studies have identified neuronal mitochondrial damage and glutamate hypertransmission in dehydrated animals. Other ways in which dehydration and fluid

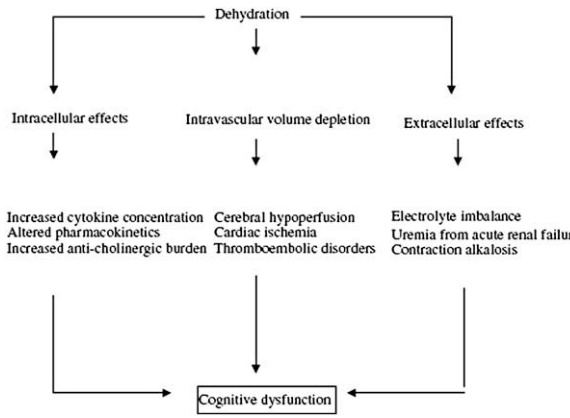

Fig. 13. Pathophysiology of cognitive dysfunction in moderate and severe dehydration. (*From* Wilson MM, Morley JE. Impaired cognitive function and mental performance in mild dehydration. Eur J Clin Nutr 2003;57(Suppl 2):S24–9; with permission.)

deficit may contribute to delirium include hypoperfusion (both cerebral and renal), increased concentration of drugs and/or their metabolites, and decreased renal elimination of drugs/metabolites and toxic by-products [340].

Similarly, it has been well documented that Na+ abnormalities, as well as other electrolytes, can lead to mental status changes and delirium. One known mechanism is that Na+ leads to cell swelling, which then causes anoxic depolarization [252]. Hypernatremic hyperosmolar delirium has been documented in medically ill and postoperative patients [352–354]. Yet, hyponatremia has been equally associated with the development of delirium, although the mechanism may not be so clearly understood [355–364].

Many have defined alterations of serum electrolytes, glucose, and renal function as both risk markers and causes of delirium [365]. Studies have suggested that a blood urea nitrogen (BUN)/creatinine ratio greater than 18 is an independent predisposing risk factor for delirium in general medical patients [339]. Elevations in BUN/creatinine may be indicative of dehydration, congestive heart failure, poor oral intake, or other factors that may contribute to the development of delirium. Others have similarly suggested that in the postoperative population a number of ''abnormal serum chemistries'' (ie, sodium <130 or >150 mEq/L; potassium <3.0 or >6.0 mEq/L; glucose <60 or >300 mg/dL) are predictable independent risk factors for postoperative delirium [366].

The EEG and delirium

Back in 1959, Engel and Romano [2] declared *''We thus arrive at the proposition that a derangement in functional metabolism underlies all instances of delirium and that this is reflected at the clinical level by the characteristic*

disturbance in cognitive functions and at the physiologic level by the characteristic slowing of the EEG''. Indeed, studies have demonstrated a very close temporal relationship between local reduction of oxygen availability and change in the EEG; the latter usually occurs 6 to 8 seconds after the local oxygen tension begins to fall [367]. In fact, both hypoxia and hypoglycemia produce slowing of the EEG [368]. These are two physiologic conditions under which it is well established that the metabolism of the brain cannot be successfully supported. EEG changes have also been described in association with anticholinergic drug–induced delirium [369].

Some have suggested that changes in EEG frequency can be demonstrated before any change in behavior or neuropsychiatric performance becomes demonstrable and well before any change in total cerebral oxygen uptake can be measured. The fundamental fact has been demonstrated that the behavioral changes correlating most precisely with the slowing of EEG frequency were those that had to do with awareness, attention, memory, and comprehension, that is, the cognitive functions [2]. Data also suggest that the significant EEG finding is *the degree of slowing rather than the absolute frequency* [370]. Thus, if the EEG initially is fast or in the upper range of normal, a significant reduction in the level of consciousness and EEG frequency may be provoked by drugs, alcohol, hypoxia, and so forth, without the EEG frequency necessarily falling below the accepted normal range. Therefore, it is therefore possible to have a ''normal EEG'' in the presence of an appreciable degree of cerebral insufficiency and reduction in the level of awareness, as when a person whose premorbid alpha frequency is t1 to t2 per second shows a slowing to 8 to 9 per second during a moderate delirium [371]. Findings confirming there are instances when the EEG may be read as ''normal'' in delirium due to a fast baseline range has been documented by others [372,373]. In these cases, a comparison with the same subject's previous EEG demonstrates the abnormality.

Others have found an association between spectral EEG changes and severity of cognitive deterioration in delirium. Spectral analysis of EEG found that delirious patients showed significant reductions of alpha percentage, increased theta and delta activity, and slowing of the peak and mean frequencies; these changes were also obvious in individual recordings. Furthermore, as previously described by Engel and Romano [2,54], the alpha percentage and various ratio parameters correlated significantly with Mini Mental State score (MMSE), and delta percentage and mean frequency with the lengths of delirium and hospitalization [55,56,374].

Similarly, serial quantitative electroencephalographic (QEEG) studies performed in elderly delirious and control subjects demonstrated that changes in scores for the relative power map and changes in relative power in the alpha band had significant associations with changes in the clinical state as measured by the MMSE [375,376]. A study of ICU patients with delirium measured the correlation between SAA (measured using a competitive radioreceptor binding assay for muscarinergic receptors) and QEEG.

During this study, delirium was diagnosed using the CAM-ICU. The results show that that under comparable conditions patients in the delirium group showed a higher relative EEG theta power and a reduced alpha power than did the nondelirious patients. On the other hand, there was no significant difference in measured SAA levels [24].

In summary, studies suggest that in the right hands the EEG could be a useful tool for the diagnosis and follow-up of delirium caused by various conditions. Conventional EEG characteristics of delirium include slowing or dropout of the posterior dominant rhythm, generalized theta or delta slow-wave activity, poor organization of the background rhythm, and loss of reactivity of the EEG to eye opening and closing. As delirium progresses, generalized theta and delta slow waves appear. When the background frequency slows to 5 or 6 Hz, loss of reactivity is seen. With further progression of delirium, generalized delta slowing appears. When any of these characteristic findings is seen, an electroencephalographer may report the presence of an "encephalopathy," which is the EEG term for global electrocerebral derangement. Sometimes triphasic waves can be seen. These are characteristic of a number of metabolic derangements (eg, hepatic failure, renal insufficiency, electrolyte abnormalities, and anoxia) [377]. These are paralleled by the QEEG findings of increased absolute and relative slow-wave (theta and delta) power, reduced ratio of fast-to-slow band power, reduced mean frequency, and reduced occipital peak frequency [56,375,376].

Finally, some have demonstrated these changes in EEG activity could be replicated by artificially increasing DA or decreasing or interfering with ACh activity, specifically in the caudate nucleus [378,379], confirming the suspicion that both decreased central cholinergic activity (either caused by hypoxia or by the use of substances with anticholinergic activity) or excess dopamine activity (caused either by hypoxia or by the exogenous use of substances) may lead to the classic behavioral manifestations of delirium and corresponding EEG changes.

Common pathways

At the end, it may very well be that all the known etiologic "factors" for the development of delirium may all act by similar mechanisms, namely causing changes to neuronal membrane function, which in turn leads to a number of neurotransmitter aberrations. Affected neurons begin to experience abnormalities of membrane function and polarization. This may lead to a domino-like effect known as "spreading depression" by which, as one neuron looses membrane integrity and stability, neighboring neurons have a more difficult time maintaining their own physiologic integrity and functioning. Some have postulated that the patterns of cerebral structure vulnerability leads to a predictable pattern of spreading neuronal depression, which causes the symptoms characteristic of delirium [1]. That progression is postulated to go from the hippocampus, to the neocortex, the subcortical

nuclei, the brain stem, gray matter, moving to the cerebellar cortex, and finally affecting the spinal cord [66,67,216].

The cholinergic and the dopaminergic systems interact not only with each other but with glutamatergic and GABA pathways. Studies suggest that excess dopamine may cause delirium and that dopaminergic antagonists are often successfully used to treat cholinergic delirium [380,381]. Furthermore, the interplay between DA and ACh in the production of delirium may be further substantiated by the fact that D2 antagonists enhance ACh release, which may be another mechanism by which they help alleviate the symptoms of delirium [382,383].

Besides the cerebral cortex, critical anatomic substrates of psychosis pathophysiology would comprise the striatum, the substantia nigra/ventral tegmental area, and the thalamus. The thalamus acts as a filter, allowing only the relevant information to travel to the cortex. Illicit drugs (eg, PCP, Ecstasy), as well as psychoactive medications frequently prescribed to hospitalized patients (eg, benzodiazepines, opioids) could compromise the thalamic gating function, leading to sensory overload and hyperarousal. Gaudreau and Gagnon [248] have proposed that drug-induced delirium would result from such transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABAergic, dopaminergic, and cholinergic pathways at critical sites of action.

Which neurotransmitter (or set of neurotransmitters) is involved, and the degree to which it may be affected, may well determine the motoric subtype that the patient presents, the degree of disorientation, and the cognitive deficits that the patient may exhibit during the episode of delirium (Table 4).

Theoretic implications for prevention and treatment options

This is meant to be a theoretic treatise on the prevention and management of delirium. For a more clinical approach, please see Maldonado JR, *Delirium in the Acute Care Setting: Characteristics, Diagnosis and Treatment,* 2008 [384].

Table 4
Neuronal circuitries and their incumbent neurotransmitters for alertness, attention, and judgment

Cognitive function	Associated neuronal circuitries
Alertness	Ascending reticular activating system Different circuitries of the brainstem
Attention	Thalamocortical loops Nondominant parietal lobe
Judgment/coherence	Diffuse cortical interconnections, somewhat more in the frontal lobes

Acetylcholine

Because of the relationship between low central ACh levels, anticholinergic potential of the medications, and delirium, it would make sense to consider two approaches that will potentially help prevent and treat delirium.

The first approach is a systematic elimination of medications, either known to cause delirium or with high anticholinergic potential, to prevent delirium, if possible. Once delirium has presented, the elimination of any potential offending agent is imperative. Switch crucial medications to other agents with the same benefits but no known anticholinergic effects. Always pay special attention to hidden anticholinergic potentials and drug-drug interactions (eg, impaired metabolism or additive effect).

Second, the use of cholinesterase inhibitors as a way to prevent or treat delirium should be considered. Indeed, acetylcholinesterase inhibitors (ACI) have a well-established use in the antagonism of neuromuscular blockade and the therapy of central anticholinergic syndrome (CAS). They also have many favorable indications such as the prevention and therapy of postanesthetic shivering and the treatment of various types of intoxication. Therefore, many have suggested that they potentially play a role in delirium prevention [385]. In particular, physostigmine, a reversible acetylcholinesterase inhibitor, has been widely used as first-line treatment of the CAS, as well as a great diagnostic and therapeutic agent for medication-induced delirium [105].

The potential usefulness in prevention of delirium with the use of ACI was demonstrated in a study using the agent rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [386]. The researchers followed men and women ($n = 246$) aged 68 to 85 years who were ambulatory outpatients who carried the diagnosis of vascular dementia (VaD). Patients were divided into two homogeneous groups matched for age and education levels. Group A received rivastigmine 3 to 6 mg/d, while Group B received cardioaspirin 100 mg/d. Patients receiving rivastigmine began treatment on the lower dose of 3 mg/d and were titrated to the higher dose of 6 mg/d after 16 weeks. All persons in the study group received periodical neurologic and neuropsychological examinations over a 24-month period. Both groups presented episodes of delirium, which occurred during a concomitant medical illness (eg, complications after a fall, during a sudden hospitalization, or after the patient received anesthesia). During the follow-up period, 48% of the entire population presented episodes of delirium. The mean duration of each episode was 7.45 ± 5.31 days. When considering the two groups separately, 40% of patients in Group A (rivastigmine group) presented episodes of delirium; whereas, 62% of patients in group B presented episodes of delirium ($P < .001$). Moreover, the mean duration of the delirium was shorter in Group A (mean duration 4.00 ± 1.71 days) than in Group B (7.86 ± 2.73 days; $P < .01$). Another study of dementia patients on chronic rivastigmine use found that the

rivastigmine group had a much lower incidence of delirium (45.5%), compared with the control group (88.9%) ($P < .05$) [387]. Nevertheless, there have been two significant failed prevention trials using the acetylcholinesterase agent, donepezil [388,389].

Finally, there have been at least 19 papers, mostly case reports, suggesting that acetylcholinesterase inhibitor agents (eg, donepezil, galantamine, physostigmine, rivastigmine) may be effective in the treatment of delirium [93,96,105,108,387,390–403].

Dopamine

Dopaminergic neurons are among the most susceptible to oxidative stress, which, as explained earlier, may lead to massive releases of DA. This in turn causes some of the classic behavioral symptoms of delirium, but it also leads to further neuronal injury. Administered DA agonist agents can produce slowing of the EEG in spite of motor hyperactivity [258] and excess dopamine is known to cause delirium [380,381].

Antipsychotic agents have long been used in the management of delirium. It is likely that initially its use was associated with the need for rapid tranquilization or neuroleptilization of agitated patients, but over time clinicians have observed a rapid restoration of putative hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis, primitive reflexes) [1]. Data suggest that depletion in DA by alphamethylparatyrosine actually protects neurons against hypoxic stress and injury [262,263]. Similarly, dopaminergic blockade can be used to reduce hypoxic damage in the hippocampus [264]. D2 antagonist agents also enhance ACh release, which may be another mechanism by which they help alleviate the symptoms of delirium [382,383]. Thus, antipsychotic agents are not only effective in the symptomatic management of the symptoms of delirium, but they also serve to address the underlying massive DA surge inherent to the etiopathological entity of delirium. In fact, clinical and experimental data suggest that neuroleptics may have a role even in the treatment of hypoactive delirium [404]. In acutely ill populations, limited data suggest that administration of antipsychotic agents with dopamine receptor antagonist activity may reduce the rate or severity of delirium [404,405].

The role of DA in facilitating GLU-mediated, Ca^{2+}-induced neuronal injury and functional derangement has been discussed earlier in this article. If that premise is correct, it is then possible that antipsychotics do much more than acute management of agitation. The exact mechanisms are not clear but, in the case of delirium, agents with DA-antagonist activity may block or reverse the DA-mediated, GLU-precipitated hypoxic neuronal injury [220]. Some data suggest that depletion of DA, as in cases of damage to the substantia nigra, may in fact protect neurons against subsequent hypoxic stress and injury [262,406].

A Cochrane database review study looking at the use antipsychotics for the treatment of delirium was conducted and included haloperidol and all atypical antipsychotics for which data have been published [407]. The studies included (n = 3) compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. The authors concluded that the decreases in delirium scores were not significantly different comparing the effect of low-dose haloperidol (<3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (odds ratio [OR] 0.63, 95% CI, 10.29–1.38; $P = .25$); and that low-dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics. Finally, low-dose haloperidol may be effective in decreasing the degree and duration of delirium in postoperative patients, compared with placebo.

Ozbolt and colleagues [408] conducted a search of the published literature using MEDLINE and PubMed for articles (in the format of review articles, randomized controlled trials [RCTs], clinical trials, or meta-analyses) written in English. They found that risperidone was the most thoroughly studied atypical antipsychotic for the management of delirium. In most studies, risperidone was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at doses of 0.5 to 4.0 mg per day. The search indicated that olanzapine was approximately 70% to 76% effective in treating the behavioral manifestations of delirium at doses of 2.5 to 11.6 mg per day. There were very few studies conducted using quetiapine; although available data suggest that it also appears to be a safe and effective alternative to high-potency antipsychotics. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects.

At least in theory, dopamine-antagonist agents should be able to prevent delirium as well. One RCT addressed the issue of prophylactic haloperidol. In at-risk patients older than 70 years, oral haloperidol 0.5 mg twice a day was administered from up to 72 hours preoperatively and until the third postoperative day. This study found that prophylactic haloperidol use did not alter the incidence of postoperative delirium (15.1%) compared with placebo (16.5%) with a relative risk (RR) = 0.91 (95% CI, 0.59–1.44) [409].

Yet another study (n = 430) demonstrated a modest reduction in the overall incidence of postoperative delirium when haloperidol was administered prophylactically (ie, 1.5 mg/d, started preoperatively and continued for up to 3 days postoperatively), with patients in the haloperidol group having a lower incidence of delirium versus placebo (15.1% versus 16.5%) (RR 0.91 [0.6–1.3]); better DRS-R-98 scores (14.4 ± 3.4 versus 18.4 ± 4.3) (mean difference 4.0 [2.0–5.8]; $P < .001$); shorter delirium duration was (5.4 days versus 11.8 days) (mean difference 6.4 days [4.0–8.0]; $P < .001$); and shorter mean length of hospital stay (17.1 ± 11.1 versus 22.6 ± 16.7) (mean difference 5.5 days [1.4–2.3]; $P < .001$). The study found no significant haloperidol-related side effects [404].

Similarly a randomized, double-blinded, placebo-controlled trial (n = 126) of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), randomly assigned patients to receive either 1 mg of risperidone or placebo sublingually upon regaining consciousness immediately postoperatively. The incidence of postoperative delirium in the risperidone group was lower than the placebo group (11.1% versus 31.7% respectively, $P = .009$, RR 0.35 [0.16–0.77]) [410]. Finally, a recently presented abstract [411] reported a significant decrease in the incidence of postoperative delirium following orthopedic joint replacement surgery (n = 400). The study compared olanzapine (5 mg Zydis formulation administered just preoperatively, and 5 mg administered immediately after surgery upon awakening) to placebo. Researchers found the incidence of delirium in the intervention group was 15%, compared with 41% in the placebo-controlled group ($P < .0001$).

Norepinephrine

As in the case of DA, acute NE (NA noradrenaline in Europe, NE norepinephrine in the United States) released secondary to hypoxia or ischemia leads to further neuronal injury and the development of worsening of delirium [412]. At least one randomized trial demonstrated that the selective alpha-2 agonist, dexmedetomidine (DEX), substantially decreased the incidence of postoperative delirium compared with conventional, GABAergic agents (3% versus 50%, respectively) [413]. It is theorized that the mechanism for the "delirium-sparring effect" is related to the receptor selectivity, absence of anticholinergic side effects, absence of respiratory depression, and potential neuron-protective effects. DEX has been shown to suppress the increase of circulating catecholamine concentrations found during cerebral ischemia [414]. In fact, one study found that, compared with placebo, DEX decreased plasma NE concentrations by 90% [415]. Another mechanism for possible neuroprotection involves its ultra-early modulation of the balance between pro- and anti-apoptotic proteins [416].

Serotonin

As previously discussed, 5-HT is toxic in elevated concentrations. High levels of 5-HT are found in cases of hepatic encephalopathy. Given its neuromodulatory effect, elevated 5-HT should be associated with hypoactive delirium.

At least one report suggests that the antiemetic agent ondansetron (ie, a selective serotonin 5-HT[3]-type receptor antagonist) may be effective in the treatment of delirium [417]. Bayindir and colleagues [417] conducted a prospective study of patients (n = 35) who developed delirium in the ICU after coronary artery bypass graft surgery. The investigators developed a behavioral scoring scale, with normal scored as 0, and severe verbal and

physical agitation was scored as 4. After a subject was determined to be delirious, the patient received a single intravenous (IV) dose of ondansetron (ie, 8 mg), and was reevaluated 10 minutes later. Before the treatment, 7 (20%) patients had a score of 2; 10 (28.6%) patients had a score of 3; and 18 (51.4%) patients had a score of 4. After the treatment, 28 (80%) patients dropped their score to 0; 6 (17.1%) patients dropped to a score of 1; and 1 (2.9%) patient remained at a score of 4. The mean score dropped from 3.20 ± 1.01 to 0.29 ± 0.75 after treatment. No adverse side effects were reported.

Glutamate and NMDA receptors

Ammonia has been recognized as an important factor in the pathogenesis of hepatic encephalopathy. Some have found that acute ammonia toxicity is mediated by activation of NMDA receptors [418]. Ischemic injury is also associated with a marked increase in extracellular GLU and activation of GLU receptors, leading to additional Ca^{2+} influx. Compounds that prevent ammonia toxicity in mice (eg, carnitine) also prevent GLU toxicity in cultured neurons. These compounds do not prevent activation of NMDA receptors or the rise of Ca^{2+}. They interfered with subsequent steps in the toxic process. The protective effect of carnitine (also known as l-carnitine or levovarnitine, is a quaternary ammonium compound biosynthesized from the amino acids lysine and methionine) is mediated by activation of metabotropic GLU receptors (mGluRs). Agonists of mGluRs, especially of mGluR5, prevent GLU toxicity. Agonists of muscarinic receptors also prevent GLU toxicity and there seems to be an interplay between muscarinic and mGluRs in the protective effect. The authors suggest that GLU toxicity can be prevented at different steps or by activating receptors coupled to the transduction pathways interfering with the toxic process.

NMDA receptors modulate learning and memory, but excessive activation leads to neuronal degeneration and cell death. Hyperammonemia and liver failure alter the function of NMDA receptors and of some associated signal transduction pathways. The function of the glutamate–nitric oxide–cGMP pathway is impaired in brain in vivo in animal models of chronic liver failure. The impairment of this pathway leads to reduced cGMP and contributes to impaired cognitive function in hepatic encephalopathy, but there is some evidence to suggest this may be restored by pharmacologic manipulation of brain cGMP, which may be achieved by administering phosphodiesterase inhibitors (zaprinast or sildenafil) or cGMP itself [277].

The alpha-a adrenoreceptor agonists (eg, DEX) has demonstrated a robust effect on neuroprotection modulated by GLU. The study compared DEX and the GLU receptor antagonist cis-4(phosphonomethyl)-2-piperidine carboxylic acid (CGS). The results demonstrated that DEX's neuroprotective efficacy was better than that produced by CGS [419].

Although the NMDA-receptor antagonist dizoclipine (MK801) has been shown to provide significant histologic neuroprotection in animal models of global cerebral ischemia [92,400,401], its clinical use in ischemic stroke has been shown to produce significant undesirable side effects (eg, delirium, psychosis, hallucinations) [420]. The NMDA/dopamine agonist agents amantadine and memantine have been used for the treatment of hypoactive-like symptoms associated with coma, traumatic brain injury, and stroke [421–423]. There are clinical data to suggest that their use may be indicated in cases of extreme psychomotor retardation, apathy, or catatonia.

Gamma-aminobutyric acid

As discussed above, GABAergic agents may lead to the development of delirium by various mechanisms. In fact, among the pharmacologic agents used in the general hospital and the critical care unit, benzodiazepine and other GABAergic agents (ie, propofol) are among the best predictors of delirium. Therefore, avoiding GABAergic agents is imperative. The only time GABAergic agents have a role in the treatment of delirium is when the mental status changes are presumed to be secondary to the withdrawal from a CNS-depressant agent (eg, alcohol, benzodiazepines, barbiturates). Otherwise, GABAergic agents should be avoided, if at all possible. This includes most commonly used sleeping aids. Please see the following section for alternate recommendations.

GABA levels are reported to be increased in patients suffering from hepatic encephalopathy. Correspondingly, at least one study found that flumazenil, a benzodiazepine antagonist, reversed coma and improved hypoactive delirium in cirrhotic patients [276].

Conversely, reduced GABA has been implicated in delirium that results from ethanol and CNS-depressant withdrawal, thus the treatment of choice for these conditions is the reintroduction of a benzodiazepine agent [424].

Sleep deprivation

The mechanism of action of most commonly used sedative agents includes either GABAergic activity or central anticholinergic effects (eg, benzodiazepine, barbiturates, propofol). Although the benzodiazepines decrease sleep latency and awakenings and increase sleep duration and efficiency (sleep duration/time in bed), these drugs also significantly reduce slow-wave and REM sleep, increase spindles, increase cortical activity at low doses, and decrease EEG amplitude at high doses [298–300]. Narcotics also suppress deep and REM sleep and increase arousals and stage-1 sleep [425].

Propofol (2,6-diisopropylphenol) is widely used in clinical anesthesia and for sedation in the ICU because of its rapid onset and clear emergence [426]. Propofol potentiates and directly activates the $GABA_A$ receptor. GABA is

the major inhibitory system in the CNS, and is involved in down-regulation of neuronal activity, including sleep [427,428].

Propofol, however, is often associated with adverse cardiovascular effects, including decreases in cardiac output and arterial blood pressure [429]. Propofol seems to have a greater depressant effect on the cardiovascular system than barbiturates. The $GABA_A$ receptor is a target of many general anesthetics, including volatile general anesthetics [430], barbiturates [431], and benzodiazepines [432], suggesting that propofol may affect the activity of the hypothalamic paraventricular nucleus.

Given the roles of melatonin in the regulation of the sleep-wake cycle, resetting of circadian rhythm disturbances and its extensive antioxidant activity have potential applications in critical care patients [433]. There are some data to suggest that exogenous melatonin supplementation may improve sleep quality and thus help prevent or alleviate delirium [121,130,139,434]. More studies are required to substantiate these claims.

DEX is a potent alpha-2 agonist agent that achieves sedation without any clinically significant respiratory depression. Thus this agent is a valuable alternative to the use of GABAergic agents (eg, benzodiazepines, propofol) to achieve adequate sedation without risk of causing or exacerbating a delirium. There are no case reports of DEX-induced delirium. On the other hand, DEX may be used to transition patients who are difficult to extubate due to agitation upon lowering of conventional sedative agents. The recommendation is to add DEX to the current sedation regimen. Once the patient has been effectively sedated for 12 to 24 hours on the combination, a slow titration of the conventional sedatives is done—the speed of this taper will depend on the sedative agent and how long has the patient been on it. This will be followed by a moderately slow titration off DEX.

Given the significant disruptions in the sleep pattern of ICU patients and the alterations in melatonin circadian rhythms, it would make sense to attempt to correct for the changes by either providing patients with sources of adequate lighting (either natural or via special lamps) or to provide melatonin supplementation. There are some, but limited data suggesting that exogenous melatonin supplementation may improve sleep quality and thus may help prevent or alleviate delirium [121,130,139,433]. More studies are needed to substantiate these claims. There are no available data on the potential use of the melatonin agonist ramelteon. As in the case of melatonin, studies are required to assess ramelteon's potential effectiveness in cases of sleep deprivation–induced delirium.

Ketamine

At least one randomized, double-blind study involving children undergoing dental repair [435] demonstrated the effectiveness of ketamine (versus placebo) for the prevention of delirium in sevoflurane-induced anesthesia using the Pediatric Anesthesia Emergence Delirium scale. The study group

exhibited a substantially lower incidence of emergence agitation (16.6%) compared with the placebo group (34.2%).

Future directions

Given the complexities already described and the multiple pathways and mechanisms that likely "go wrong together" or "cause a domino-like" effect, it would make sense to consider a treatment strategy that addresses all these factors simultaneously. Unfortunately, there are very limited data to support any of these approaches, let alone in combination. But only well-designed treatment trials will be able to determine whether the theory bears out in clinical success. The basic approach of treating delirium may consider the neurochemical underpinnings described earlier. Thus, in treating an acutely delirious individual we should consider restoring adequate function of all recognized dysfunctional pathways. How to effectively do that, to prevent neurochemical derangement or restore adequate functioning, should be the focus of future studies.

Summary

Delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, cognition, orientation, attention, psychomotor activity, sleep-wake cycle, and behavior. Delirium is likely to be the most common and the most serious complication in the medically ill, particularly the elderly and the critically ill. Not only does it cause distress to patients, families, and medical caregivers, but its presence is associated with increased morbidity and mortality, prolonged hospital stays, poor functional and cognitive recovery, increased placement in specialized intermediate and long-term care facilities, and increased cost of care.

It is unlikely that we will ever be able to find a single cause of delirium, or a single pathway leading to delirium. Nevertheless, the better we are able to understand how multiple clinical or environmental factors influence brain chemistry and functioning, the better we will be able to understand the complex sets of neurochemical cascades that are set in motion and that manifest themselves in the symptoms of delirium. If we truly get to understand the pathophysiological mechanisms that, working together, lead to the disordered brain function that causes delirium, we may be able to find evidence-based medication treatments or environmental manipulations that address each and every one of them to shorten the course of the syndrome. More importantly, given the recognized long-term cognitive and functional effects of delirium, we should eventually strive to find ways to prevent its development altogether. Given the complexities of the human brain and the many intricacies in the interacting pathways that likely help the brain function properly or go awry, we have a better chance of

effectively preventing and treating delirium by implementing multilevel approaches that address the many pathways described in this article.

Acknowledgment

The author thanks Emma Bakes, MS for her assistance in locating, reviewing and helping select many of the papers referenced throughout the manuscript. The author also acknowledges the thoughtful suggestions of Gregory Kapinos, MD particularly in the area of hypoxia & hypoperfusion, as well as his critique of the original manuscript.

References

[1] Brown T. Basic mechanisms in the pathogenesis of delirium. In: Stoudemire A, Greenberg DB, editors. The Psychiatric Care of the Medical Patient. 2nd edition. New York: Oxford Press; 2000. p. 571–80.
[2] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. J Chronic Dis 1959; 9(3):260–77.
[3] Lipowski ZJ. Update on delirium. Psychiatr Clin North Am 1992;15(2):335–46.
[4] Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994;42(8):809–15.
[5] Inouye S, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113(12):941–8.
[6] Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27(12):1892–900.
[7] Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. J Geriatr Psychiatry Neurol 1998;11(3):118–25, discussion 157–8.
[8] Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. Jama 2004;291(14):1753–62.
[9] Inouye SK. Delirium in hospitalized older patients. Clin Geriatr Med 1998;14(4):745–64.
[10] Levkoff SE, Evans DA, Liptzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med 1992;152(2):334–40.
[11] Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32(4):955–62.
[12] Murray AM, Levkoff SE, Wetle TT, et al. Acute delirium and functional decline in the hospitalized elderly patient. J Gerontol 1993;48(5):M181–6.
[13] Ebert AD, Walzer TA, Huth C, et al. Early neurobehavioral disorders after cardiac surgery: a comparative analysis of coronary artery bypass graft surgery and valve replacement. J Cardiothorac Vasc Anesth 2001;15(1):15–9.
[14] O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 1997;45(2):174–8.
[15] Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. Jama 1990;263(8):1097–101.
[16] Shinn JA, Maldonado JR. Performance improvement: increasing recognition and treatment of postoperative delirium. Prog Cardiovasc Nurs 2000;15(3):114–5.
[17] Gibson GE, Blass JP. Impaired synthesis of acetylcholine in brain accompanying mild hypoxia and hypoglycemia. J Neurochem 1976;27(1):37–42.
[18] Flacker JM, Cummings V, Mach JR Jr, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6(1):31–41.
[19] Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 1999;54(6):B239–46.

[20] Trzepacz PT. The neuropathogenesis of delirium. A need to focus our research. Psychosomatics 1994;35(4):374–91.
[21] Beresin EV. Delirium in the elderly. J Geriatr Psychiatry Neurol 1988;1(3):127–43.
[22] Flacker JM, Wei JY. Endogenous anticholinergic substances may exist during acute illness in elderly medical patients. J Gerontol A Biol Sci Med Sci 2001;56(6):M353–5.
[23] Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987;144(9):1218–20.
[24] Plaschke K, Thomas C, Engelhardt R, et al. Significant correlation between plasma and CSF anticholinergic activity in presurgical patients. Neurosci Lett 2007;417(1):16–20.
[25] Trzepacz PT. Anticholinergic Model For Delirium. Semin Clin Neuropsychiatry 1996;1(4): 294–303.
[26] Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000;5(2):132–48.
[27] Tune LE, Bylsma FW, Hilt DC. Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. J Neuropsychiatry Clin Neurosci 1992;4(2):195–7.
[28] Tune LE, Egeli S. Acetylcholine and delirium. Dement Geriatr Cogn Disord 1999;10(5): 342–4.
[29] Milstein A, Pollack A, Kleinman G, et al. Confusion/delirium following cataract surgery: an incidence study of 1-year duration. Int Psychogeriatr 2002;14(3):301–6.
[30] Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):21–6.
[31] Lowery DP, Wesnes K, Ballard CG. Subtle attentional deficits in the absence of dementia are associated with an increased risk of post-operative delirium. Dement Geriatr Cogn Disord 2007;23(6):390–4.
[32] Gibson GE, Peterson C, Jenden DJ. Brain acetylcholine synthesis declines with senescence. Science 1981;213(4508):674–6.
[33] Gibson GE, Peterson C. Aging decreases oxidative metabolism and the release and synthesis of acetylcholine. J Neurochem 1981;37(4):978–84.
[34] Gibson GE, Peterson C. Acetylcholine and oxidative metabolism in septum and hippocampus in vitro. J Biol Chem 1983;258(2):1142–5.
[35] Jansson A, Olin K, Yoshitake T, et al. Effects of isoflurane on prefrontal acetylcholine release and hypothalamic Fos response in young adult and aged rats. Exp Neurol 2004; 190(2):535–43.
[36] Gibson GE, Peterson C. Decreases in the release of acetylcholine in vitro with low oxygen. Biochem Pharmacol 1982;31(1):111–5.
[37] Gibson GE, Peterson C, Sansone J. Decreases in amino acids and acetylcholine metabolism during hypoxia. J Neurochem 1981;37(1):192–201.
[38] Blass J, Gibson G, Duffy T, et al. Cholinergic dysfunction: a common denominator in metabolic encephalopathies. In: Pepeu G, Ladinsky H, editors. Cholinergic Machanisms. New York, NY: Plenum Publishing Corp.; 1981. p. 921–8.
[39] Brown T, Stoudemire A. Antipsychotics. Psychiatric Side Effects of Prescription and Over-the-Counter Medications. Washington, DC: American Psychiatric Press; 1998. p. 3-33.
[40] Bergmann K, Eastham EJ. Psychogeriatric ascertainment and assessment for treatment in an acute medical ward setting. Age Ageing 1974;3(3):174–88.
[41] Wacker P, Nunes PV, Cabrita H, et al. Post-operative delirium is associated with poor cognitive outcome and dementia. Dement Geriatr Cogn Disord 2006;21(4):221–7.
[42] Wahlund L, Bjorlin GA. Delirium in clinical practice: experiences from a specialized delirium ward. Dement Geriatr Cogn Disord 1999;10(5):389–92.
[43] Tune L, Coyle JT. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. Arch Gen Psychiatry 1980;37(3):293–7.
[44] Tune LE, Damlouji NF, Holland A, et al. Association of postoperative delirium with raised serum levels of anticholinergic drugs. Lancet 1981;2(8248):651–3.

[45] Thomas RI, Cameron DJ, Fahs MC. A prospective study of delirium and prolonged hospital stay. Exploratory study. Arch Gen Psychiatry 1988;45(10):937–40.
[46] Mussi C, Ferrari R, Ascari S, et al. Importance of serum anticholinergic activity in the assessment of elderly patients with delirium. J Geriatr Psychiatry Neurol 1999;12(2):82–6.
[47] Mach JR Jr, Dysken MW, Kuskowski M, et al. Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. J Am Geriatr Soc 1995;43(5):491–5.
[48] Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). Jama 2001;286(21):2703–10.
[49] Mulsant BH, Pollock BG, Kirshner M, et al. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. Arch Gen Psychiatry 2003;60(2):198–203.
[50] Trzepacz PT, Leavitt M, Ciongoli K. An animal model for delirium. Psychosomatics 1992; 33(4):404–15.
[51] Lipowski ZJ. Delirium (acute confusional states). Jama 1987;258(13):1789–92.
[52] Fatranska M, Budai D, Oprsalova Z, et al. Acetylcholine and its enzymes in some brain areas of the rat under stress. Brain Res 1987;424(1):109–14.
[53] Takayama H, Mizukawa K, Ota Z, et al. Regional responses of rat brain muscarinic cholinergic receptors to immobilization stress. Brain Res 1987;436(2):291–5.
[54] Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. 1959. J Neuropsychiatry Clin Neurosci 2004;16(4):526–38.
[55] Koponen H, Hurri L, Stenback U, et al. Computed tomography findings in delirium. J Nerv Ment Dis 1989;177(4):226–31.
[56] Koponen H, Partanen J, Paakkonen A, et al. EEG spectral analysis in delirium. J Neurol Neurosurg Psychiatry 1989;52(8):980–5.
[57] Koponen H, Stenback U, Mattila E, et al. Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one-year follow-up. Acta Psychiatr Scand 1989;79(6):579–85.
[58] Plaschke K, Hill H, Engelhardt R, et al. EEG changes and serum anticholinergic activity measured in patients with delirium in the intensive care unit. Anaesthesia 2007;62(12):1217–23.
[59] Romano J, Engel G. Delirium. I. EEG data. Arch Neurol Psychiatry 1944;51:356–77.
[60] Trzepacz PT, Sclabassi RJ, Van Thiel DH. Delirium: a subcortical phenomenon? J Neuropsychiatry Clin Neurosci 1989;1(3):283–90.
[61] Rouatbi S, Dardouri K, Farhat Ouahchi Y, et al. [Aging of the lung parenchyma]. Rev Mal Respir 2006;23(5 Pt 1):445–52 [French].
[62] Kaye DM, Esler MD. Autonomic Control of the Aging Heart. Neuromolecular Med 2008, in press.
[63] Miyamoto E, Tomimoto H, Nakao Si S, et al. Caudoputamen is damaged by hypocapnia during mechanical ventilation in a rat model of chronic cerebral hypoperfusion. Stroke 2001;32(12):2920–5.
[64] Roman GC. Brain hypoperfusion: a critical factor in vascular dementia. Neurol Res 2004; 26(5):454–8.
[65] Aliev G, Obrenovich ME, Smith MA, et al. Hypoperfusion, Mitochondria Failure, Oxidative Stress, and Alzheimer Disease. J Biomed Biotechnol 2003;2003(3):162–3.
[66] Bures J, Buresova O, Krivanek J. The meaning and significance of Leao's spreading depression. An Acad Bras Cienc 1984;56(4):385–400.
[67] Czeh G, Somjen GG. Hypoxic failure of synaptic transmission in the isolated spinal cord, and the effects of divalent cations. Brain Res 1990;527(2):224–33.
[68] Nicoll RA, Malenka RC, Kauer JA. Functional comparison of neurotransmitter receptor subtypes in mammalian central nervous system. Physiol Rev 1990;70(2):513–65.
[69] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. Jama 1996; 275(11):852–7.

[70] Gaudreau JD, Gagnon P, Roy MA, et al. Association between psychoactive medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005;46(4):302–16.
[71] Tune L, Carr S, Cooper T, et al. Association of anticholinergic activity of prescribed medications with postoperative delirium. J Neuropsychiatry Clin Neurosci 1993;5(2):208–10.
[72] Brauer C, Morrison RS, Silberzweig SB, et al. The cause of delirium in patients with hip fracture. Arch Intern Med 2000;160(12):1856–60.
[73] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43(3):183–94.
[74] Tuma R, DeAngelis LM. Altered mental status in patients with cancer. Arch Neurol 2000; 57(12):1727–31.
[75] Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 2000;160(6):786–94.
[76] Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 2001;22(6):997–1006.
[77] Olofsson SM, Weitzner MA, Valentine AD, et al. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. Support Care Cancer 1996; 4(5):351–7.
[78] Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. Jama 2002;287(3):345–55.
[79] Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 2006;102(4):1255–66.
[80] Gaudreau JD, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. Cancer 2007;109(11):2365–73.
[81] Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006;102(4):1267–73.
[82] Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother 2007;21(1):15–25.
[83] Wang Y, et al. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry 2007;15(1):50–9.
[84] Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med 2004; 18(3):184–94.
[85] Dubois MJ, Bergeron N, Dumont M, et al. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 2001;27(8):1297–304.
[86] Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999;10(5):393–400.
[87] Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. Am J Med 1999;106(5):565–73.
[88] Eisendrath SJ, Goldman B, Douglas J, et al. Meperidine-induced delirium. Am J Psychiatry 1987;144(8):1062–5.
[89] Marcantonio ER, et al. The relationship of postoperative delirium with psychoactive medications. Jama 1994;272(19):1518–22.
[90] Stock SL, Catalano G, Catalano MC. Meperidine associated mental status changes in a patient with chronic renal failure. J Fla Med Assoc 1996;83(5):315–9.
[91] Bruera E, Pereira J. Acute neuropsychiatric findings in a patient receiving fentanyl for cancer pain. Pain 1997;69(1-2):199–201.
[92] Bruera E, Strasser F, Shen L, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage 2003; 26(5):1049–54.
[93] Vigano A, Fan D, Bruera E. Individualized use of methadone and opioid rotation in the comprehensive management of cancer pain associated with poor prognostic indicators. Pain 1996;67(1):115–9.

[94] Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161(8):1099–105.
[95] Kobayashi K, Higashima M, Mutou K, et al. Severe delirium due to basal forebrain vascular lesion and efficacy of donepezil. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28(7):1189–94.
[96] Milusheva E, Sperlagh B, Kiss B, et al. Inhibitory effect of hypoxic condition on acetylcholine release is partly due to the effect of adenosine released from the tissue. Brain Res Bull 1990;24(3):369–73.
[97] Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001; 62(Suppl. 21):11–4.
[98] Tune L, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992;149(10):1393–4.
[99] Tune LE. Serum anticholinergic activity levels and delirium in the elderly. Semin Clin Neuropsychiatry 2000;5(2):149–53.
[100] Tune L, Folstein MF. Post-operative delirium. Adv Psychosom Med 1986;15:51–68.
[101] Landi F, Russo A, Liperoti R, et al. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 2007;81(2):235–41.
[102] Blass JP, Gibson GE. Cerebrometabolic aspects of delirium in relationship to dementia. Dement Geriatr Cogn Disord 1999;10(5):335–8.
[103] Meuret P, Backman SB, Bonhomme V, et al. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 2000;93(3):708–17.
[104] Beaver KM, Gavin TJ. Treatment of acute anticholinergic poisoning with physostigmine. Am J Emerg Med 1998;16(5):505–7.
[105] Haase U, Rundshagen I. [Pharmacotherapy–physostigmine administered post-operatively]. Anasthesiol Intensivmed Notfallmed Schmerzther 2007;42(3):188–9 [German].
[106] Holinger PC, Klawans HL. Reversal of tricyclic-overdosage-induced central anticholinergic syndrome by physostigmine. Am J Psychiatry 1976;133(9):1018–23.
[107] Richardson WH 3rd, Williams SR, Carstairs SD. A picturesque reversal of antimuscarinic delirium. J Emerg Med 2004;26(4):463.
[108] Weizberg M, Su M, Mazzola JL, et al. Altered mental status from olanzapine overdose treated with physostigmine. Clin Toxicol (Phila) 2006;44(3):319–25.
[109] Francis J, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. J Am Geriatr Soc 1992;40(6):601–6.
[110] Trzepacz PT. Update on the neuropathogenesis of delirium. Dement Geriatr Cogn Disord 1999;10(5):330–4.
[111] BaHammam A. Sleep in acute care units. Sleep Breath 2006;10(1):6–15.
[112] Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. Neuron 2004;44(1):121–33.
[113] Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol 2006;57:139–66.
[114] Yoo SS, et al. A deficit in the ability to form new human memories without sleep. Nat Neurosci 2007;10(3):385–92.
[115] Dinges DF, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997;20(4):267–77.
[116] Dinges DF. The state of sleep deprivation: From functional biology to functional consequences. Sleep Med Rev 2006;10(5):303–5.
[117] Yoo SS, Gujar N, Hu P, et al. The human emotional brain without sleep–a prefrontal amygdala disconnect. Curr Biol 2007;17(20):R877–8.
[118] Berger M, Vollmann J, Hohagen F, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. Am J Psychiatry 1997;154(6):870–2.

[119] Evans JI, Lewis SA. Sleep studies in early delirium and during drug withdrawal in normal subjects and the effect of phenothiazines on such states. Electroencephalogr Clin Neurophysiol 1968;25(5):508–9.
[120] Johns M, Large AA, Masterton JP, et al. Sleep and delirium after open heart surgery. Br J Surg 1974;61(5):377–81.
[121] Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the Intensive Care Unit. Minerva Anestesiol 2008;74(6):329–33.
[122] Bergamasco B, Brignolio F, Doriguzzi T, et al. [Longitudinal polygraphic study of sleep in 11 patients with delirium tremens. Physiopathological considerations on ''sleep deprivation'']. Acta Neurol (Napoli) 1968;23(2):289–99 [Italian].
[123] Ito H, Harada D, Hayashida K, et al. [Psychiatry and sleep disorders–delirium]. Seishin Shinkeigaku Zasshi 2006;108(11):1217–21 [Japanese].
[124] Lee JW. Recurrent delirium associated with obstructive sleep apnea. Gen Hosp Psychiatry 1998;20(2):120–2.
[125] Munoz X, Marti S, Sumalla J, et al. Acute delirium as a manifestation of obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1998;158(4):1306–7.
[126] Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. Crit Care Clin 2006;22(2):313–27, vii.
[127] Whitney JF, Gannon DE. Obstructive sleep apnea presenting as acute delirium. Am J Emerg Med 1996;14(3):270–1.
[128] Heller SS, Frank KA, Malm JR, et al. Psychiatric complications of open-heart surgery. A re-examination. N Engl J Med 1970;283(19):1015–20.
[129] Helton MC, Gordon SH, Nunnery SL. The correlation between sleep deprivation and the intensive care unit syndrome. Heart Lung 1980;9(3):464–8.
[130] Miyazaki T, Kuwano H, Kato H, et al. Correlation between serum melatonin circadian rhythm and intensive care unit psychosis after thoracic esophagectomy. Surgery 2003; 133(6):662–8.
[131] Misra S, Ganzini L. Delirium, depression, and anxiety. Crit Care Clin 2003;19(4):771–87, viii.
[132] Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Br Med J (Clin Res Ed) 1985;290(6474):1029–32.
[133] Simini B. Patients' perceptions of intensive care. Lancet 1999;354(9178):571–2.
[134] Cooper AB, Thornley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. Chest 2000;117(3):809–18.
[135] Freedman NS, Gazendam J, Levan L, et al. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med 2001;163(2):451–7.
[136] Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. Sleep 2006;29(5):707–16.
[137] Shigeta H, Yasui A, Nimura Y, et al. Postoperative delirium and melatonin levels in elderly patients. Am J Surg 2001;182(5):449–54.
[138] Balan S, Leibovitz A, Zila SO, et al. The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. J Neuropsychiatry Clin Neurosci 2003;15(3): 363–6.
[139] Olofsson K, Alling C, Lundberg D, et al. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. Acta Anaesthesiol Scand 2004;48(6):679–84.
[140] Krueger JM, Majde JA. Humoral links between sleep and the immune system: research issues. Ann N Y Acad Sci 2003;992:9–20.
[141] Ozturk L, Pelin Z, Karadeniz D, et al. Effects of 48 hours sleep deprivation on human immune profile. Sleep Res Online 1999;2(4):107–11.
[142] Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. Jama 2002;288(12):1471–2.

[143] Irwin M, McClintick J, Costlow C, et al. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. Faseb J 1996;10(5):643–53.
[144] Leproult R, Copinschi G, Buxton O, et al. Sleep loss results in an elevation of cortisol levels the next evening. Sleep 1997;20(10):865–70.
[145] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354(9188):1435–9.
[146] Litaker D, Locala J, Franco K, et al. Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 2001;23(2):84–9.
[147] Ouimet S, Kavanagh BP, Gottfried SB, et al. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 2007;33(1):66–73.
[148] Hala M. Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. Med Hypotheses 2007; 68(1):194–6.
[149] Kalman J, Juhasz A, Bogats G, et al. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. Neurochem Int 2006;48(3):177–80.
[150] Ramlawi B, Rudolph JL, Mieno S, et al. Surgery. C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery 2006;140(2): 221–6.
[151] Ramlawi B, Rudolph JL, Mieno S, et al. Serologic markers of brain injury and cognitive function after cardiopulmonary bypass. Ann Surg 2006;244(4):593–601.
[152] Becher B, Bechmann I, Greter M. Antigen presentation in autoimmunity and CNS inflammation: how T lymphocytes recognize the brain. J Mol Med 2006;84(7):532–43.
[153] Dimitrijevic OB, Stamatovic SM, Keep RF, et al. Effects of the chemokine CCL2 on blood-brain barrier permeability during ischemia-reperfusion injury. J Cereb Blood Flow Metab 2006;26(6):797–810.
[154] Mahad D, Callahan MK, Williams KA, et al. Modulating CCR2 and CCL2 at the blood-brain barrier: relevance for multiple sclerosis pathogenesis. Brain 2006;129(Pt 1): 212–23.
[155] Ubogu EE, Callahan MK, Tucky BH, et al. CCR5 expression on monocytes and T cells: modulation by transmigration across the blood-brain barrier in vitro. Cell Immunol 2006;243(1):19–29.
[156] Ubogu EE, et al. Determinants of CCL5-driven mononuclear cell migration across the blood-brain barrier. Implications for therapeutically modulating neuroinflammation. J Neuroimmunol 2006;179(1-2):132–44.
[157] Jeppsson B, Freund HR, Gimmon Z, et al. Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? Am J Surg 1981;141(1):136–42.
[158] Holmes JH, Connolly NC, Paull DL, et al. Magnitude of the inflammatory response to cardiopulmonary bypass and its relation to adverse clinical outcomes. Inflamm Res 2002; 51(12):579–86.
[159] Roth-Isigkeit A, Borstel TV, Seyfarth M, et al. Perioperative serum levels of tumour-necrosis-factor alpha (TNF-alpha), IL-1 beta, IL-6, IL-10 and soluble IL-2 receptor in patients undergoing cardiac surgery with cardiopulmonary bypass without and with correction for haemodilution. Clin Exp Immunol 1999;118(2):242–6.
[160] de Rooij SE, van Munster, B C, Korevaar JC, et al. Cytokines and acute phase response in delirium. J Psychosom Res 2007;62(5):521–5.
[161] Adamis D, Treloar A, Martin FC, et al. Int J Geriatr Psychiatry. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients 2007; 22(7):688–94.
[162] Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci 2007;62(4): 420–6.

[163] Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. J Gerontol A Biol Sci Med Sci 2008;63(2):184–9.
[164] van der Mast RC, Fekkes D. Serotonin and amino acids: partners in delirium pathophysiology? Semin Clin Neuropsychiatry 2000;5(2):125–31.
[165] Fries M, Bickenbach J, Henzler D, et al. S-100 protein and neurohistopathologic changes in a porcine model of acute lung injury. Anesthesiology 2005;102(4):761–7.
[166] Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984;5(1):25–44.
[167] Seckl JR, Olsson T. Glucocorticoid hypersecretion and the age-impaired hippocampus: cause or effect? J Endocrinol 1995;145(2):201–11.
[168] Basavaraju N, Phillips SL. Cortisol deficient state. A cause of reversible cognitive impairment and delirium in the elderly. J Am Geriatr Soc 1989;37(1):49–51.
[169] McIntosh TK, Bush HL, Yeston NS, et al. Beta-endorphin, cortisol and postoperative delirium: a preliminary report. Psychoneuroendocrinology 1985;10(3):303–13.
[170] Robertsson B, Blennow K, Brane G, et al. Hyperactivity in the hypothalamic-pituitary-adrenal axis in demented patients with delirium. Int Clin Psychopharmacol 2001;16(1):39–47.
[171] Olsson T, Marklund N, Gustafson Y, et al. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. Stroke 1992;23(11):1573–6.
[172] Olsson T. Urinary free cortisol excretion shortly after ischaemic stroke. J Intern Med 1990; 228(2):177–81.
[173] Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. Dement Geriatr Cogn Disord 1999;10(5):345–9.
[174] De Kloet ER, Vreugdenhil E, Oitzl MS, et al. Brain corticosteroid receptor balance in health and disease. Endocr Rev 1998;19(3):269–301.
[175] Sapolsky RM. Why stress is bad for your brain. Science 1996;273(5276):749–50.
[176] Sapolsky RM, Krey LC, McEwen BS. Stress down-regulates corticosterone receptors in a site-specific manner in the brain. Endocrinology 1984;114(1):287–92.
[177] Demonacos CV, Karayanni N, Hatzoglou E, et al. Mitochondrial genes as sites of primary action of steroid hormones. Steroids 1996;61(4):226–32.
[178] Agardh CD, Siesjo BK. Hypoglycemic brain injury: phospholipids, free fatty acids, and cyclic nucleotides in the cerebellum of the rat after 30 and 60 minutes of severe insulin-induced hypoglycemia. J Cereb Blood Flow Metab 1981;1(3):267–75.
[179] Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. Brain Cogn 1995;28(3):240–58.
[180] Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 1991;12(2):118–34.
[181] Fischette CT, Komisaruk BR, Edinger HM, et al. Differential fornix ablations and the circadian rhythmicity of adrenal corticosteroid secretion. Brain Res 1980;195(2):373–87.
[182] Rubin RT, Mandell AJ, Crandall PH. Corticosteroid responses to limbic stimulation in man: localization of stimulus sites. Science 1966;153(737):767–8.
[183] van der Mast RC, Fekkes D, Moleman P, et al. Is postoperative delirium related to reduced plasma tryptophan? Lancet 1991;338(8771):851–2.
[184] Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological regulation by plasma neutral amino acids. Science 1972;178(59):414–6.
[185] Kaufman S. An evaluation of the possible neurotoxicity of metabolites of phenylalanine. J Pediatr 1989;114(5):895–900.
[186] van der Mast RC, van den Broek WW, Fekkes D, et al. Delirium after cardiac surgery. The possible role of tryptophan in relation to the other neutral aminoacids. Adv Exp Med Biol 1996;398:93–6.
[187] Mizock BA, Sabelli HC, Dubin A, et al. Septic encephalopathy. Evidence for altered phenylalanine metabolism and comparison with hepatic encephalopathy. Arch Intern Med 1990;150(2):443–9.

[188] Takezawa J, Taenaka N, Nishijima MK, et al. Amino acids and thiobarbituric acid reactive substances in cerebrospinal fluid and plasma of patients with septic encephalopathy. Crit Care Med 1983;11(11):876–9.
[189] Krause W, Halminski M, McDonald L, et al. Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria. A model for the study of phenylalanine and brain function in man. J Clin Invest 1985;75(1):40–8.
[190] Krause W, Epstein C, Averbook A, et al. Phenylalanine alters the mean power frequency of electroencephalograms and plasma L-dopa in treated patients with phenylketonuria. Pediatr Res 1986;20(11):1112–6.
[191] Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. J Gerontol A Biol Sci Med Sci 2000;55(5):B249-52; discussion B253–4.
[192] Blum D, Maldonado J, Meyer E, et al. Delirium following abrupt discontinuation of fluoxetine. Clin Neurol Neurosurg 2008;110(1):69–70.
[193] Black K, Shea C, Dursun S, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 2000;25(3):255–61.
[194] Fava M, Mulroy R, Alpert J, et al. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry 1997;154(12):1760–2.
[195] Broderick PA, Gibson GE. Dopamine and serotonin in rat striatum during in vivo hypoxic-hypoxia. Metab Brain Dis 1989;4(2):143–53.
[196] Freund HR, Fischer JE. The use of branched chain amino acids (BCAA) in acute hepatic encephalopathy. Clin Nutr 1986;5(3):135–8.
[197] Freund HR, Muggia-Sullam M, LaFrance R, et al. Regional brain amino acid and neurotransmitter derangements during abdominal sepsis and septic encephalopathy in the rat. The effect of amino acid infusions. Arch Surg 1986;121(2):209–16.
[198] Knell AJ, Davidson AR, Williams R, et al. Dopamine and serotonin metabolism in hepatic encephalopathy. Br Med J 1974;1(5907):549–51.
[199] Harrison MJ, Marsden CD, Jenner P. Effect of experimental ischemia on neurotransmitter amines in the gerbil brain. Stroke 1979;10(2):165–8.
[200] Shimizu-Sasamata M, Bosque-Hamilton P, Huang PL, Moskowitz MA, E.H.. Lo, Attenuated neurotransmitter release and spreading depression-like depolarizations after focal ischemia in mutant mice with disrupted type I nitric oxide synthase gene. J Neurosci 1998;18(22):9564–71.
[201] Zivin JA, Stashak J. The effect of ischemia on biogenic amine concentrations in the central nervous system. Stroke 1983;14(4):556–62.
[202] Beisel W, Wannemacher RW, Neufield HA. Relation of fever to energy expenditure. In: Kinney J, Lense E, editors. Assessment of Energy Metabolism in Health and Disease. Columbus (OH): Ross Laboratories; 2000. p. 144–50.
[203] Fine A, Anderson NL, Rothstein TL, et al. Fas expression in pulmonary alveolar type II cells. Am J Physiol 1997;273(1 Pt 1):L64–71.
[204] Kinney JM, Duke JH Jr, Long CL, et al. Tissue fuel and weight loss after injury. J Clin Pathol Suppl (R Coll Pathol) 1970;4:65–72.
[205] McGee W, Veremakis C, Wilson GL. Clinical importance of tissue oxygenation and use to the mixed venous blood gas. Res Medica 1988;4(2):15–24.
[206] Weissman C, Kemper M, Damask MC, et al. Effect of routine intensive care interactions on metabolic rate. Chest 1984;86(6):815–8.
[207] Rossen R, Kabat H, Anderson JP. Acute arrest of cerebral circulation in man. Arch Neurol Psychiatry 1943;50:510–28.
[208] Cole SL, Corday E. Four-minute limit for cardiac resuscitation. J Am Med Assoc 1956; 161(15):1454–8.
[209] Corday E, Rothenberg S, Weiner SM. Cerebral vascular insufficiency; an explanation of the transient stroke. AMA Arch Intern Med 1956;98(6):683–90.
[210] Pena F, Ramirez JM. Hypoxia-induced changes in neuronal network properties. Mol Neurobiol 2005;32(3):251–83.

[211] Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin 2006;24(1):1–21.
[212] Basarsky TA, Feighan D, MacVicar BA. Glutamate release through volume-activated channels during spreading depression. J Neurosci 1999;19(15):6439–45.
[213] Iijima T, Shimase C, Iwao Y, et al. Relationships between glutamate release, blood flow and spreading depression: real-time monitoring using an electroenzymatic dialysis electrode. Neurosci Res 1998;32(3):201–7.
[214] Moghaddam B, Schenk JO, Stewart WB, et al. Temporal relationship between neurotransmitter release and ion flux during spreading depression and anoxia. Can J Physiol Pharmacol 1987;65(5):1105–10.
[215] Somjen GG, Aitken PG, Balestrino M, et al. Extracellular ions, hypoxic irreversible loss of function and delayed postischemic neuron degeneration studied in vitro. Acta Physiol Scand Suppl 1989;582:58.
[216] Somjen GG, et al. Spreading depression-like depolarization and selective vulnerability of neurons. A brief review. Stroke 1990;21(11 Suppl):III179–83.
[217] Busto R, Dietrich WD, Globus MY, et al. Extracellular release of serotonin following fluid-percussion brain injury in rats. J Neurotrauma 1997;14(1):35–42.
[218] Busto R, Globus MY, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989;20(7): 904–10.
[219] Globus MY, Alonso O, Dietrich WD, et al. Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. J Neurochem 1995;65(4): 1704–11.
[220] Globus MY, Busto R, Dietrich WD, et al. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. J Neurochem 1988;51(5):1455–64.
[221] Globus MY, et al. Intra-ischemic extracellular release of dopamine and glutamate is associated with striatal vulnerability to ischemia. Neurosci Lett 1988;91(1):36–40.
[222] Globus MY, et al. Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. J Cereb Blood Flow Metab 1989;9(6): 892–6.
[223] Globus MY, Busto R, Martinez E, et al. Ischemia induces release of glutamate in regions spared from histopathologic damage in the rat. Stroke 1990;21(11 Suppl):III43–6.
[224] Globus MY, Wester P, Busto R, et al. Ischemia-induced extracellular release of serotonin plays a role in CA1 neuronal cell death in rats. Stroke 1992;23(11):1595–601.
[225] Takagi K, Ginsberg MD, Globus MY, et al. Effect of hyperthermia on glutamate release in ischemic penumbra after middle cerebral artery occlusion in rats. Am J Physiol 1994;(5 Pt 2):267:H1770–6.
[226] Siesjo BK. Cerebral circulation and metabolism. J Neurosurg 1984;60(5):883–908.
[227] Kirsch JR, Diringer MN, Borel CO, et al. Brain resuscitation. Medical management and innovations. Crit Care Nurs Clin North Am 1989;1(1):143–54.
[228] Choi DW. Calcium-mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. Trends Neurosci 1988;11(10):465–9.
[229] Choi DW, Weiss JH, Koh JY, et al. Glutamate neurotoxicity, calcium, and zinc. Ann N Y Acad Sci 1989;568:219–24.
[230] Katayama Y, Kawamata T, Tamura T, et al. Calcium-dependent glutamate release concomitant with massive potassium flux during cerebral ischemia in vivo. Brain Res 1991; 558(1):136–40.
[231] Graham DG. Catecholamine toxicity: a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease. Neurotoxicology 1984;5(1):83–95.
[232] Bertrand N, Bralet J, Beley A. Post-ischemic regional changes in acetylcholine synthesis following transient forebrain ischemia in gerbils. Neurochem Res 1992;17(4):321–5.

[233] Hirsch JA, Gibson GE. Selective alteration of neurotransmitter release by low oxygen in vitro. Neurochem Res 1984;9(8):1039–49.
[234] Hirsch JA, Gibson GE. Thiamin antagonists and the release of acetylcholine and norepinephrine from brain slices. Biochem Pharmacol 1984;33(14):2325–7.
[235] Siesjo BK. Brain energy metabolism and catecholaminergic activity in hypoxia, hypercapnia and ischemia. J Neural Transm 1978;14(Suppl):17–22.
[236] Seaman JS, Schillerstrom J, Carroll D, et al. Impaired oxidative metabolism precipitates delirium: a study of 101 ICU patients. Psychosomatics 2006;47(1):56–61.
[237] Rosenberg J, Kehlet H. Postoperative mental confusion–association with postoperative hypoxemia. Surgery 1993;114(1):76–81.
[238] Kim HC, Young T, Matthews CG, et al. Sleep-disordered breathing and neuropsychological deficits. A population-based study. Am J Respir Crit Care Med 1997;156(6): 1813–9.
[239] Grant I, Heaton RK, McSweeny AJ, et al. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1982;142(8):1470–6.
[240] Aakerlund LP, Rosenberg J. Postoperative delirium: treatment with supplementary oxygen. Br J Anaesth 1994;72(3):286–90.
[241] Maekawa T, Fujii Y, Sadamitsu D, et al. Cerebral circulation and metabolism in patients with septic encephalopathy. Am J Emerg Med 1991;9(2):139–43.
[242] Blomqvist P, Wieloch T. Ischemic brain damage in rats following cardiac arrest using a long-term recovery model. J Cereb Blood Flow Metab 1985;5(3):420–31.
[243] Takemoto O, Tomimoto H, Yanagihara T. Induction of c-fos and c-jun gene products and heat shock protein after brief and prolonged cerebral ischemia in gerbils. Stroke 1995;26(9): 1639–48.
[244] Adams J, Brierley JB, Connor RC, et al. The effects of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. Brain 1966;89(2): 235–68.
[245] Auer R, Benveniste H. Hypoxia and related conditions. In: Graham D, Lantos PL, editors. Greenfield's Neuropathology. New York: Oxford University Press; 1997. p. 263–314.
[246] Margerison JH, Corsellis JA, Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain 1966;89(3):499–530.
[247] Ng T, Graham DI, Adams JH, et al. Changes in the hippocampus and the cerebellum resulting from hypoxic insults: frequency and distribution. Acta Neuropathol 1989;78(4): 438–43.
[248] Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. Med Hypotheses 2005;64(3):471–5.
[249] Sommer BR, Wise LC, Kraemer HC. Is dopamine administration possibly a risk factor for delirium? Crit Care Med 2002;30(7):1508–11.
[250] Carmen JS, Wyatt RJ. Calcium and malignant catatonia. Lancet 1977;2(8048):1124–5.
[251] Nagatsu T. Genes for human catecholamine-synthesizing enzymes. Neurosci Res 1991; 12(2):315–45.
[252] Balestrino M. Pathophysiology of anoxic depolarization: new findings and a working hypothesis. J Neurosci Methods 1995;59(1):99–103.
[253] Katz IR. Oxygen dependence of dopamine-beta-hydoxylase activity and lactate metabolism in synaptosomes from rat brain. Brain Res 1982;231(2):399–409.
[254] Pulsinelli WA, Duffy TE. Regional energy balance in rat brain after transient forebrain ischemia. J Neurochem 1983;40(5):1500–3.
[255] Trouvin JH, Prioux-Guyonneau M, Cohen Y, et al. Rat brain monoamine metabolism and hypobaric hypoxia: a new approach. Gen Pharmacol 1986;17(1):69–73.
[256] Miller R. Major psychosis and dopamine: controversial features and some suggestions. Psychol Med 1984;14(4):779–89.

[257] Figiel GS, Krishnan KR, Doraiswamy PM. Subcortical structural changes in ECT-induced delirium. J Geriatr Psychiatry Neurol 1990;3(3):172–6.
[258] Ongini E, Caporali MG, Massotti M. Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. Life Sci 1985;37(24): 2327–33.
[259] Cassem N, Murray GB, Lafayette JM, et al. Delirious patients. In: Stern T, Fricchione GL, Cassem NH, Jellinek MS, Rosenbaum JF, Littleton MA, editors. Massachusetts General Handbook of General Hospital Psychiatry. Littleton (MA): PSG Publishing Co; 2004. p. 119–34.
[260] Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161: 843–5.
[261] Pedrosa R, Soares-da-Silva P. Oxidative and non-oxidative mechanisms of neuronal cell death and apoptosis by L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine. Br J Pharmacol 2002;137(8):1305–13.
[262] Globus MY, Ginsberg MD, Dietrich WD, et al. Substantia nigra lesion protects against ischemic damage in the striatum. Neurosci Lett 1987;80(3):251–6.
[263] Weinberger J, Nieves-Rosa J, Cohen G. Nerve terminal damage in cerebral ischemia: protective effect of alpha-methyl-para-tyrosine. Stroke 1985;16(5):864–70.
[264] Globus MY. Role of dopamine in ischemic neuronal damage. Stroke 1989;20(6):827–8.
[265] Katayama Y, Tamura T, Becker DP, et al. Calcium-dependent component of massive increase in extracellular potassium during cerebral ischemia as demonstrated by microdialysis in vivo. Brain Res 1991;567(1):57–63.
[266] Freeman GB, Mykytyn V, Gibson GE. Differential alteration of dopamine, acetylcholine, and glutamate release during anoxia and/or 3,4-diaminopyridine treatment. Neurochem Res 1987;12(11):1019–27.
[267] Reid AA, Monn JA, Jacobson AE, et al. Characterization of NMDA-coupled and dopamine reuptake carrier coupled [3H]-TCP binding sites in guinea pig brain. NIDA Res Monogr 1989;95:530–1.
[268] Rothman SM, Olney JW. Excitotoxicity and the NMDA receptor–still lethal after eight years. Trends Neurosci 1995;18(2):57–8.
[269] Rothman SM, Yamada KA, Lancaster N. Nordihydroguaiaretic acid attenuates NMDA neurotoxicity–action beyond the receptor. Neuropharmacology 1993;32(11):1279–88.
[270] Rothman S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. J Neurosci 1984;4(7):1884–91.
[271] Yamada KA, Rothman SM. Diazoxide blocks glutamate desensitization and prolongs excitatory postsynaptic currents in rat hippocampal neurons. J Physiol 1992;458: 409–23.
[272] Lopes da Silva FH, Witter MP, Boeijinga PH, et al. Anatomic organization and physiology of the limbic cortex. Physiol Rev 1990;70(2):453–511.
[273] Bokesch PM, Izykenova GA, Justice JB, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. Stroke 2006;37(6):1432–6.
[274] Huda A, Guze BH, Thomas A, et al. Clinical correlation of neuropsychological tests with 1H magnetic resonance spectroscopy in hepatic encephalopathy. Psychosom Med 1998; 60(5):550–6.
[275] Weinberger DR. A connectionist approach to the prefrontal cortex. J Neuropsychiatry Clin Neurosci 1993;5(3):241–53.
[276] Howard CD, Seifert CF. Flumazenil in the treatment of hepatic encephalopathy. Ann Pharmacother 1993;27(1):46–8.
[277] Llansola M, Rodrigo R, Monfort P, et al. NMDA receptors in hyperammonemia and hepatic encephalopathy. Metab Brain Dis 2007;22(3-4):321–35.
[278] Baldy-Moulinier M, Bories P. CBF and metabolism in hepatic encephalopathy: effects of acute hyperammoneamia and of L. dopa. Acta Neurol Scand Suppl 1977;64:348–9.

[279] Aggarwal S, Obrist W, Yonas H, et al. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: relationship to outcome. Liver Transpl 2005;11(11):1353–60.
[280] O'Beirne JP, Chouhan M, Hughes RD. The role of infection and inflammation in the pathogenesis of hepatic encephalopathy and cerebral edema in acute liver failure. Nat Clin Pract Gastroenterol Hepatol 2006;3(3):118–9.
[281] Saksena S, Rai V, Saraswat VA, et al. Cerebral diffusion tensor imaging and in vivo proton magnetic resonance spectroscopy in patients with fulminant hepatic failure. J Gastroenterol Hepatol 2007, in press.
[282] Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. Dan Med Bull 2007;54(2):99–111.
[283] Strauss GI, Moller K, Larsen FS, et al. Cerebral glucose and oxygen metabolism in patients with fulminant hepatic failure. Liver Transpl 2003;9(12):1244–52.
[284] Trzepacz PT, Tarter RE, Shah A, et al. SPECT scan and cognitive findings in subclinical hepatic encephalopathy. J Neuropsychiatry Clin Neurosci 1994;6(2):170–5.
[285] Naegele T, Grodd W, Viebahn R, et al. MR imaging and (1)H spectroscopy of brain metabolites in hepatic encephalopathy: time-course of renormalization after liver transplantation. Radiology 2000;216(3):683–91.
[286] Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. Cochrane Database Syst Rev 2004;(2):CD002798.
[287] Basile AS, Harrison PM, Hughes RD, et al. Relationship between plasma benzodiazepine receptor ligand concentrations and severity of hepatic encephalopathy. Hepatology 1994; 19(1):112–21.
[288] Butterworth RF. Hepatic encephalopathy: a neuropsychiatric disorder involving multiple neurotransmitter systems. Curr Opin Neurol 2000;13(6):721–7.
[289] Butterworth RF. Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. Metab Brain Dis 2001;16(1-2):55–65.
[290] Ferenci P, Schafer DF, Kleinberger G, et al. Serum levels of gamma-aminobutyric-acid-like activity in acute and chronic hepatocellular disease. Lancet 1983;2(8354):811–4.
[291] Aliyev NA, Aliyev ZN, Aliguliyev AR. Amino acid neurotransmitters in alcohol withdrawal. Alcohol Alcohol 1994;29(6):643–7.
[292] Akaike N, Shirasaki T, Yakushiji T. Quinolones and fenbufen interact with GABAA receptor in dissociated hippocampal cells of rat. J Neurophysiol 1991;66(2):497–504.
[293] Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20): 1471–7.
[294] Kudoh A, Takase H, Takahira Y, et al. Postoperative confusion increases in elderly long-term benzodiazepine users. Anesth Analg 2004;99(6):1674–8 [table of contents].
[295] Tune LE, Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. Int Psychogeriatr 1991;3(2):397–408.
[296] Pain L, Jeltsch H, Lehmann O, et al. Central cholinergic depletion induced by 192 IgG-saporin alleviates the sedative effects of propofol in rats. Br J Anaesth 2000;85(6): 869–73.
[297] Wang Y, Kikuchi T, Sakai M, et al. Age-related modifications of effects of ketamine and propofol on rat hippocampal acetylcholine release studied by in vivo brain microdialysis. Acta Anaesthesiol Scand 2000;44(1):112–7.
[298] Achermann P, Borbely AA. Hum Neurobiol. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics 1987;6(3): 203–10.
[299] Borbely AA, Mattmann P, Loepfe M, et al. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. Hum Neurobiol 1985;4(3):189–94.
[300] Qureshi A, Lee-Chiong T Jr. Medications and their effects on sleep. Med Clin North Am 2004;88(3):751–66, x.

[301] Zhu H, Cottrell JE, Kass IS. The effect of thiopental and propofol on NMDA- and AMPA-mediated glutamate excitotoxicity. Anesthesiology 1997;87(4):944–51.
[302] Crews FT, Morrow AL, Criswell H, et al. Effects of ethanol on ion channels. Int Rev Neurobiol 1996;39:283–367.
[303] Nevo I, Hamon M. Neurotransmitter and neuromodulatory mechanisms involved in alcohol abuse and alcoholism. Neurochem Int 1995;26(4):305–36, discussion 337–42.
[304] Tollefson GD. Serotonin and alcohol: interrelationships. Psychopathology 1989; 22(Suppl. 1):37–48.
[305] Smith AJ, Brent PJ, Henry DA, et al. Plasma noradrenaline, platelet alpha 2-adrenoceptors, and functional scores during ethanol withdrawal. Alcohol Clin Exp Res 1990;14(4): 497–502.
[306] Patkar AA, Gopalakrishnan R, Naik PC, et al. Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. Alcohol Alcohol 2003;38(3):224–31.
[307] Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science 1989;243(4899):1721–4.
[308] Lovinger DM, White G, Weight FF. NMDA receptor-mediated synaptic excitation selectively inhibited by ethanol in hippocampal slice from adult rat. J Neurosci 1990;10(4):1372–9.
[309] Carta M, Ariwodola OJ, Weiner JL, et al. Alcohol potently inhibits the kainate receptor-dependent excitatory drive of hippocampal interneurons. Proc Natl Acad Sci U S A 2003;100(11):6813–8.
[310] Lovinger DM, White G. Ethanol potentiation of 5-hydroxytryptamine3 receptor-mediated ion current in neuroblastoma cells and isolated adult mammalian neurons. Mol Pharmacol 1991;40(2):263–70.
[311] Davies M. The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. J Psychiatry Neurosci 2003;28(4):263–74.
[312] Mihic SJ, Ye Q, Wick MJ, et al. Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. Nature 1997;389(6649):385–9.
[313] Kobayashi T, Ikeda K, Kojima H, et al. Ethanol opens G-protein-activated inwardly rectifying K+ channels. Nat Neurosci 1999;2(12):1091–7.
[314] Walter HJ, Messing RO. Regulation of neuronal voltage-gated calcium channels by ethanol. Neurochem Int 1999;35(2):95–101.
[315] Pirker S, Schwarzer C, Wieselthaler A, et al. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 2000;101(4):815–50.
[316] Rogawski MA. Update on the neurobiology of alcohol withdrawal seizures. Epilepsy Curr 2005;5(6):225–30.
[317] Whittington MA, Lambert JD, Little HJ. Increased NMDA receptor and calcium channel activity underlying ethanol withdrawal hyperexcitability. Alcohol Alcohol 1995;30(1): 105–14.
[318] Hoffman P, Grant KA, Snell LD, et al. NMDA receptors: role in ethanol withdrawal seizures. Ann N Y Acad Sci 1992;654:52–60.
[319] Grant KA, Valverius P, Hudspith M, et al. Ethanol withdrawal seizures and the NMDA receptor complex. Eur J Pharmacol 1990;176(3):289–96.
[320] Hoffman P, Rabe CS, Grant KA, et al. Ethanol and the NMDA receptor. Alcohol 1990; 7(3):229–31.
[321] Grant KA, Snell LD, Rogawski MA, et al. Comparison of the effects of the uncompetitive N-methyl-D-aspartate antagonist (±)-5-aminocarbonyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine (ADCI) with its structural analogs dizocilpine (MK-801) and carbamazepine on ethanol withdrawal seizures. J Pharmacol Exp Ther 1992; 260(3):1017–22.
[322] Faingold C, Li Y, Evans MS. Decreased GABA and increased glutamate receptor-mediated activity on inferior colliculus neurons in vitro are associated with susceptibility to ethanol withdrawal seizures. Brain Res 2000;868(2):287–95.

[323] Fujimoto A, Nagao T, Ebara T, et al. Cerebrospinal fluid monoamine metabolites during alcohol withdrawal syndrome and recovered state. Biol Psychiatry 1983;18(10):1141–52.
[324] Hawley RJ, Major LF, Schulman EA, et al. Cerebrospinal fluid 3-methoxy-4-hydroxyphenylglycol and norepinephrine levels in alcohol withdrawal. Correlations with clinical signs. Arch Gen Psychiatry 1985;42(11):1056–62.
[325] Berggren U, Fahlke C, Norrby A, et al. Subsensitive alpha-2-adrenoceptor function in male alcohol-dependent individuals during 6 months of abstinence. Drug Alcohol Depend 2000; 57(3):255–60.
[326] Nutt D, Glue P, Molyneux S, et al. Alpha-2-adrenoceptor function in alcohol withdrawal: a pilot study of the effects of iv. clonidine in alcoholics and normals. Alcohol Clin Exp Res 1988;12(1):14–8.
[327] Ballenger JC, Goodwin FK, Major LF, et al. Alcohol and central serotonin metabolism in man. Arch Gen Psychiatry 1979;36(2):224–7.
[328] Krystal JH, Webb E, Cooney NL, et al. Serotonergic and noradrenergic dysregulation in alcoholism: m-chlorophenylpiperazine and yohimbine effects in recently detoxified alcoholics and healthy comparison subjects. Am J Psychiatry 1996;153(1):83–92.
[329] Schwartz JC, et al. Histamine receptors in the brain: characterization by binding studies and biochemical effects. Adv Biochem Psychopharmacol 1980;21:169–82.
[330] Schwartz JC, Arrang JM, Garbarg M, et al. Properties and roles of the three subclasses of histamine receptors in brain. J Exp Biol 1986;124:203–24.
[331] White JM, Rumbold GR. Behavioural effects of histamine and its antagonists: a review. Psychopharmacology (Berl) 1988;95(1):1–14.
[332] Sitter H, Lorenz W, Klotter HJ, et al. Elevated plasma histamine concentration as a sensitive real-time parameter for distinct phases of surgical trauma: a tool for technology assessment. Agents Actions 1991;33(1-2):203–7.
[333] Adachi N, Oishi R, Saeki K. Changes in the metabolism of histamine and monoamines after occlusion of the middle cerebral artery in rats. J Neurochem 1991;57(1):61–6.
[334] Fujitani T, Adachi N, Nagaro T, et al. Histaminergic H2 action protects hippocampal CA1 neurons by prolonging the onset of the anoxic depolarization in gerbils. J Neurochem 1996; 67(6):2613–5.
[335] Koponen H, Reinikainen K, Riekkinen PJ. Cerebrospinal fluid somatostatin in delirium. II. Changes at the acute stage and at one year follow-up. Psychol Med 1990;20(3):501–5.
[336] Koponen HJ, Leinonen E, Lepola U, et al. A long-term follow-up study of cerebrospinal fluid somatostatin in delirium. Acta Psychiatr Scand 1994;89(5):329–34.
[337] Koponen H, Stenback U, Mattila E, et al. CSF beta-endorphin-like immunoreactivity in delirium. Biol Psychiatry 1989;25(7):938–44.
[338] Koponen H, Riekkinen J. A longitudinal study of cerebrospinal fluid beta-endorphin-like immunoreactivity in delirium: changes at the acute stage and at one-year follow-up. Acta Psychiatr Scand 1990;82(4):323–6.
[339] Inouye S, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119(6): 474–81.
[340] Lawlor PG. Delirium and dehydration: some fluid for thought? Support Care Cancer 2002; 10(6):445–54.
[341] Seymour DG, Henschke PJ, Cape RD, et al. Acute confusional states and dementia in the elderly: the role of dehydration/volume depletion, physical illness and age. Age Ageing 1980;9(3):137–46.
[342] Wilson MM, Morley JE. Impaired cognitive function and mental performance in mild dehydration. Eur J Clin Nutr 2003;57(Suppl. 2):S24–9.
[343] Rolls BJ, Phillips PA. Aging and disturbances of thirst and fluid balance. Nutr Rev 1990; 48(3):137–44.
[344] Silver AJ. Aging and risks for dehydration. Cleve Clin J Med 1990;57(4):341–4.

[345] George J, Rockwood K. Dehydration and delirium–not a simple relationship. J Gerontol A Biol Sci Med Sci 2004;59(8):811–2.
[346] Reyes-Ortiz CA. Dehydration, delirium, and disability in elderly patients. Jama 1997; 278(4):287–8.
[347] Stiefel F. Delirium and dehydration: inevitable companions of terminal disease? Support Care Cancer 2002;10(6):443–4.
[348] Miller DK, Perry HM 3rd, Morley JE. Nestle Nutr Workshop Ser Clin Perform Programme. Associations among the Mini Nutritional Assessment instrument, dehydration, and functional status among older African Americans in St. Louis, Mo., USA. 1999;1: 79–86.
[349] Warren JL, Bacon WE, Harris T, et al. The burden and outcomes associated with dehydration among US elderly, 1991. Am J Public Health 1994;84(8):1265–9.
[350] Gopinathan PM, Pichan G, Sharma VM. Role of dehydration in heat stress-induced variations in mental performance. Arch Environ Health 1988;43(1):15–7.
[351] Cian C, Barraud PA, Melin B, et al. Effects of fluid ingestion on cognitive function after heat stress or exercise-induced dehydration. Int J Psychophysiol 2001;42(3):243–51.
[352] Giltay EJ, Huijskes RV, Kho KH, et al. Psychotic symptoms in patients undergoing coronary artery bypass grafting and heart valve operation. Eur J Cardiothorac Surg 2006;30(1): 140–7.
[353] Hiramatsu Y, Sakakibara Y, Mitsui T, et al. [Clinical features of hypernatremic hyperosmolar delirium following open heart surgery]. Nippon Kyobu Geka Gakkai Zasshi 1991; 39(10):1945–8 [Japanese].
[354] Mattle H. [Neurologic manifestations of osmolality disorders]. Schweiz Med Wochenschr 1985;115(26):882–9 [German].
[355] Aldemir M, Ozen S, Kara IH, et al. Predisposing factors for delirium in the surgical intensive care unit. Crit Care 2001;5(5):265–70.
[356] Bartoli E, Castello L, Sainaghi PP. [Diagnosis and therapy of hyponatremia]. Ann Ital Med Int 2003;18(4):193–203 [Italian].
[357] Chuang YF, Chiu YL, Hwang TJ, et al. Delirium and multiple electrolyte abnormalities associated with high dose paroxetine exposure. Psychiatry Clin Neurosci 2006;60(5): 642–3.
[358] Croxson M, Lucas J, W. Bagg. Diluting delirium. N Z Med J 2005;118(1222):U1661.
[359] Gunther A, Rauch M, Krumpelmann U, et al. [Hyponatraemic delirium as an early symptom of small-cell bronchial carcinoma]. Nervenarzt 2003;74(11):1016–9.
[360] Ladino M, Guardiola VD, Paniagua M. Mirtazapine-induced hyponatremia in an elderly hospice patient. J Palliat Med 2006;9(2):258–60.
[361] Huguenard P. [Delirium provoked by intravenous therapy without sodium.]. Anesth Anal 1956;13(3):592–7 [French].
[362] Welti W. Delirium with low serum sodium. AMA Arch Neurol Psychiatry 1956;76(5): 559–64.
[363] Rai A, Whaley-Connell A, McFarlane S, et al. Hyponatremia, arginine vasopressin dysregulation, and vasopressin receptor antagonism. Am J Nephrol 2006;26(6):579–89.
[364] Zaluska M, Janota B, Papierska L. [Personality and behavioural disturbances, with delusional-hallucinatory and delirium episodes in the course of hyponatremia due to paraneoplastic inappropriate vasopressin secretion (SIADH)]. Psychiatr Pol 2006;40(6):1149–60 [Polish].
[365] Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 1998;13(3):204–12.
[366] Marcantonio ER, et al. A clinical prediction rule for delirium after elective noncardiac surgery. Jama 1994;271(2):134–9.
[367] Meyer JS, Fang HC, Denny-Brown D. Polarographic study of cerebral collateral circulation. AMA Arch Neurol Psychiatry 1954;72(3):296–312.

[368] Gibbs FA, Williams D, Gibbs EL. Modification of the Cortical Frequency Spectrum by Changes in Carbon Dioxide, Blood Sugar, and Oxygen. J Neurophysiol 1940;3:49.
[369] Itil T, Fink M. Anticholinergic drug-induced delirium: experimental modification, quantitative EEG and behavioral correlations. J Nerv Ment Dis 1966;143(6):492–507.
[370] Engel GL, Webb JP, Ferris EB. Quantitative Electroencephalographic Studies of Anoxia in Humans; Comparison with Acute Alcoholic Intoxication and Hypoglycemia. J Clin Invest 1945;24(5):691–7.
[371] Engel GL, Romano J, Ferris EB. Variations in the Normal Electroencephalogram During a Five-Year Period. Science 1947;105(2736):600–1.
[372] Pro JD, Wells CE. The use of the electroencephalogram in the diagnosis of delirium. Dis Nerv Syst 1977;38(10):804–8.
[373] Trzepacz PT, Meagher DJ, Lafayette JM, et al. Neuropsychiatric aspects of delirium. In: Yudofsky SC, Hales RE, editors. Textbook of Neuropsychiatry. Washington, DC: American Psychiatric Press; 2008. p. 445–518.
[374] Koponen H. Electroencephalographic indices for diagnosis of delirium. Int Psychogeriatr 1991;3(2):249–51.
[375] Jacobson SA, Leuchter AF, Walter DO. Conventional and quantitative EEG in the diagnosis of delirium among the elderly. J Neurol Neurosurg Psychiatry 1993;56(2):153–8.
[376] Jacobson S, Leuchter AF, Walter DO, et al. Serial quantitative EEG among elderly subjects with delirium. Biol Psychiatry 1993;34(3):135–40.
[377] Jacobson S, Jerrier H. EEG in delirium. Semin Clin Neuropsychiatry 2000;5(2):86–92.
[378] Keane PE, Hall RC. The effect of acetylcholine and dopamine on the caudate spindle in cats. J Neurosci Res 1977;3(3):209–16.
[379] Keane PE, Neal H. The effect of injections of dopaminergic agonists into the caudate nucleus on the electrocorticogram of the rat. J Neurosci Res 1981;6(2):237–41.
[380] Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153(2):231–7.
[381] Platt MM, Breitbart W, Smith M, et al. Efficacy of neuroleptics for hypoactive delirium. J Neuropsychiatry Clin Neurosci 1994;6(1):66–7.
[382] Ikarashi Y, Takahashi A, Ishimaru H, et al. Regulation of dopamine D1 and D2 receptors on striatal acetylcholine release in rats. Brain Res Bull 1997;43(1):107–15.
[383] Ikarashi Y, Takahashi A, Ishimaru H, et al. Suppression of cholinergic activity via the dopamine D2 receptor in the rat striatum. Neurochem Int 1997;30(2):191–7.
[384] Maldonado J. Delirium in the Acute Care Setting: Characteristics, Diagnosis & Treatment. Critical Care Clinics 2008;24:657–720.
[385] Kleinschmidt S, Ziegeler S, Bauer C. [Cholinesterase inhibitors. Importance in anaesthesia, intensive care medicine, emergency medicine and pain therapy]. Anaesthesist 2005;54(8): 791–9 [German].
[386] Moretti R, Torre P, Antonello RM, et al. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. Am J Alzheimers Dis Other Demen 2004;19(6):333–9.
[387] Dautzenberg PL, Mulder LJ, Rikkert Olde, et al. Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage. Int J Geriatr Psychiatry 2004; 19(7):641–4.
[388] Liptzin B, Laki A, Garb JL, et al. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry 2005;13(12):1100–6.
[389] Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry 2007;22(4):343–9.
[390] Baraka A, Harik S. Reversal of central anticholinergic syndrome by galanthamine. Jama 1977;238(21):2293–4.

[391] Burt T. Donepezil and related cholinesterase inhibitors as mood and behavioral controlling agents. Curr Psychiatry Rep 2000;2(6):473–8.
[392] Fisher RS, Bortz JJ, Blum DE, et al. A Pilot Study of Donepezil for Memory Problems in Epilepsy. Epilepsy Behav 2001;2(4):330–4.
[393] Gleason OC. Donepezil for postoperative delirium. Psychosomatics 2003;44(5):437–8.
[394] Hori K, Tominaga I, Inada T, et al. Donepezil-responsive alcohol-related prolonged delirium. Psychiatry Clin Neurosci 2003;57(6):603–4.
[395] Kaufer DI, Catt KE, Lopez OL, et al. Dementia with Lewy bodies: response of delirium-like features to donepezil. Neurology 1998;51(5):1512.
[396] Logan CJ, Stewart JT. Treatment of post-electroconvulsive therapy delirium and agitation with donepezil. J Ect 2007;23(1):28–9.
[397] Moretti R, Torre P, Antonello RM, et al. Rivastigmine in frontotemporal dementia: an open-label study. Drugs Aging 2004;21(14):931–7.
[398] Noyan MA, Elbi H, Aksu H. Donepezil for anticholinergic drug intoxication: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(5):885–7.
[399] Palmer TR. Donepezil in advanced dementia, or delirium? J Am Med Dir Assoc 2004;5(1): 67.
[400] Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. J Pain Symptom Manage 2004;27(3):268–73.
[401] Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. J Am Geriatr Soc 1999;47(3):379–80.
[402] Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. J Geriatr Psychiatry Neurol 1998;11(3): 159–61.
[403] van den Bliek BM, Maas HA. [Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine]. Ned Tijdschr Geneeskd 2004;148(43):2149. [author reply 2149] [Dutch].
[404] Kalisvaart K, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53(10):1658–66.
[405] Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004;30(3):444–9.
[406] Globus MY, Ginsberg MD, Harik SI, et al. Role of dopamine in ischemic striatal injury: metabolic evidence. Neurology 1987;37(11):1712–9.
[407] Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. Cochrane Database Syst Rev 2007;(2):CD005594.
[408] Ozbolt LB, Paniagua MA, Kaiser RM. Atypical antipsychotics for the treatment of delirious elders. J Am Med Dir Assoc 2008;9(1):18–28.
[409] Schrader SL, Wellik KE, Demaerschalk BM, et al. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. Neurologist 2008;14(2):134–7.
[410] Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007;35(5):714–9.
[411] Larsen KA, Kelly S, Stern TA. A double-blind, randomized, placebo-controlled study of peri-operative administration of olanzapine to prevent post-operative delirium in joint replacement patients. Presented at the Annual Meeting of the Academy of Psychosomatic Medicine. Amalia Island, FL: 2007.
[412] Bhardwaj A, Brannan T, Martinez-Tica J, et al. Ischemia in the dorsal hippocampus is associated with acute extracellular release of dopamine and norepinephrine. J Neural Transm Gen Sect 1990;80(3):195–201.
[413] Maldonado J, van der Starre P, Wysong A, et al. Dexmedetomidine: Can it reduce the incidence of ICU delirium in postcardiotomy patients? Psychosomatics 2004;45(2):173.

[414] Engelhard K, Werner C, Kaspar S, et al. Effect of the alpha2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. Anesthesiology 2002;96(2):450–7.
[415] Jalonen J, Hynynen M, Kuitunen A, et al. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. Anesthesiology 1997;86(2):331–45.
[416] Engelhard K, Werner C, Eberspacher E, et al. The effect of the alpha 2-agonist dexmedetomidine and the N-methyl-D-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats. Anesth Analg 2003;96(2):524–31. [table of contents].
[417] Bayindir O, Guden M, Akpinar B, et al. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. J Thorac Cardiovasc Surg 2001; 121(1):176–7.
[418] Felipo V, Hermenegildo C, Montoliu C, et al. Neurotoxicity of ammonia and glutamate: molecular mechanisms and prevention. Neurotoxicology 1998;19(4-5): 675–81.
[419] Jolkkonen J, Puurunen K, Koistinaho J, et al. Neuroprotection by the alpha2-adrenoceptor agonist, dexmedetomidine, in rat focal cerebral ischemia. Eur J Pharmacol 1999;372(1): 31–6.
[420] Rossberg M, Bhardwaj A, Hurn PD, et al. Principles of cerebroprotection. In: Murray M, Coursin DB, Pearl RG, et al, editors. Critical care medicine: perioperative management. Philadelphia: Lipincott Williams & Williams; 2002. p. 225–35.
[421] Chandler MC, Barnhill JL, Gualtieri CT. Amantadine for the agitated head-injury patient. Brain Inj 1988;2(4):309–11.
[422] Edby K, Larsson J, Eek M, et al. Amantadine treatment of a patient with anoxic brain injury. Childs Nerv Syst 1995;11(10):607–9.
[423] Van Reekum R, Bayley M, Garner S, et al. N of 1 study: amantadine for the amotivational syndrome in a patient with traumatic brain injury. Brain Inj 1995;9(1):49–53.
[424] Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Jama 1997;278(2): 144–51.
[425] Cronin AJ, Keifer JC, Davies MF, et al. Postoperative sleep disturbance: influences of opioids and pain in humans. Sleep 2001;24(1):39–44.
[426] Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism–an overview. Postgrad Med J 1985;61(Suppl. 3):45–50.
[427] Concas A, Santoro G, Mascia MP, et al. The general anesthetic propofol enhances the function of gamma-aminobutyric acid-coupled chloride channel in the rat cerebral cortex. J Neurochem 1990;55(6):2135–8.
[428] Sanna E, Garau F, Harris RA. Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: actions of the anesthetics propofol and pentobarbital. Mol Pharmacol 1995;47(2):213–7.
[429] Ebert TJ, Muzi M. Propofol and autonomic reflex function in humans. Anesth Analg 1994; 78(2):369–75.
[430] Yang J, Isenberg KE, Zorumski CF. Volatile anesthetics gate a chloride current in postnatal rat hippocampal neurons. Faseb J 1992;6(3):914–8.
[431] Nicoll RA, Wojtowicz JM. The effects of pentobarbital and related compounds on frog motoneurons. Brain Res 1980;191(1):225–37.
[432] Study RE, Barker JL. Diazepam and (–)-pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of gamma-aminobutyric acid responses in cultured central neurons. Proc Natl Acad Sci U S A 1981;78(11):7180–4.
[433] Bourne RS, Mills GH. Melatonin: possible implications for the postoperative and critically ill patient. Intensive Care Med 2006;32(3):371–9.

[434] Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg 2002;94(2):338–9. [table of contents].
[435] Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. Paediatr Anaesth 2007;17(9):846–50.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 857–874

CRITICAL
CARE
CLINICS

Mood Disorders and the Outcome of Suicidal Thoughts and Attempts

Steven L. Dubovsky, MD[a,b,*],
Amelia N. Dubovsky, MD[c]

[a]*Department of Psychiatry, University at Buffalo, 462 Grider Street, Room 1182, Buffalo, NY 14215–3098, USA*
[b]*Psychiatry and Medicine, University of Colorado School of Medicine, 4200 E. 9 Avenue, Denver, CO, USA*
[c]*Harvard University, 55 Fruit Street, Bullfinch 440 and 441, Boston, MA 02215, USA*

Suicidal ideation and attempts are common reasons for visits to the emergency department and critical care hospitalizations and a common public health problem. Most patients who make a suicide attempt have a psychiatric disorder, most frequently a mood, psychotic, substance use, or personality disorder. Demographic factors are not reliable predictors of a repeat attempt in an individual patient, but regret at having survived, a viable plan that the patient has rehearsed, severe depression with anxiety, command hallucinations, and ongoing substance use increase the risk substantially, as do a past and family history of depression. Patients who are at high risk of another attempt and cannot be transferred promptly to a psychiatric service should be managed jointly by the psychiatric and critical care teams with an emphasis on protection of the patient, identification of substance intoxication and withdrawal, making the environment safe, and instituting treatment of the psychiatric disorder. Antidepressants reduce suicide risk but their slow onset of action may make electroconvulsive therapy a desirable alternative for severely depressed patients. Parenteral treatment is possible with benzodiazepines and antipsychotic drugs but not antidepressants.

Suicidality in adults

In 2003 (the latest year for which figures are available), more than 400,000 episodes of deliberate self-harm, about 60% of which are believed

* Corresponding author. Department of Psychiatry, University at Buffalo, 462 Grider Street, Room 1182, Buffalo, NY 14215–3098.
E-mail address: dubovsky@buffalo.edu (S.L. Dubovsky).

0749-0704/08/$ - see front matter
doi:10.1016/j.ccc.2008.05.002 *criticalcare.theclinics.com*

to be suicide attempts, were treated in emergency departments in the United States [1]. In the general population, the incidence of suicide attempts is estimated at 67 to 151 per 100,000 [2]. The actual number of suicides and suicide attempts is undoubtedly underestimated, however, because many are reported as accidents or undetermined deaths [3]. Suicidal ideation can be identified in as many as 7% of primary care patients [4].

The lifetime prevalence of nonfatal suicide attempts has been estimated at 3% to 5% of the general United States population and as much as 16% of community samples with a diagnosis of major depressive disorder [1]. Suicide attempts tend to be repeated throughout the patient's life, especially in the presence of substance abuse and impulsivity [1]. In community samples, about 5% of people who develop depression commit suicide [5], whereas the suicide rate is as high as 15% in depressed patients treated in clinical settings. Another study found that only 3% of depressed patients who committed suicide had received adequate pharmacotherapy and only 7% received weekly psychotherapy [6].

Most people who commit suicide have a psychiatric illness, the most common diagnoses being depression, schizophrenia, substance abuse, and personality disorders, often in combination [7,8]. Over a third of patients who receive treatment in the emergency department for a suicide attempt carry a diagnosis of major depressive disorder at the time of the attempt [1]. More severe depression is associated with more suicide attempts [1]. Most suicide attempts occur early in the course of a depressive episode and are associated with escalating hopelessness and isolation [1]. Comorbid anxiety seems to increase the risk of suicide in depressed patients [9].

Suicide is frequently thought to be limited to more severely ill patients in psychiatric settings. Nevertheless, the federally sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that depressed patients in primary care practice had the same level of severity as a sample of patients (N = 2541) with nonpsychotic major depressive disorder [10]. In the same sample, a history of attempted suicide was reported by 13% of depressed patients in primary care and 18% of those in specialty care. Similarly, 43% of depressed primary care patients and 51% of specialty care patients reported feeling that "life was not worth living" the week before the assessment. A family history of suicide was reported in 3% of depressed patients in each setting [10].

Among 4037 enrollees in the STAR*D study, 16.5% reported previous suicide attempts [1]. Controlling for age, gender, and depressive symptom severity, previous attempters had more current general medical conditions ($P < .0001$), more current alcohol and substance abuse ($P < .0001$), more work hours missed in the past week (26.2% versus 18.2%, $P < .0001$), and more current suicidal ideation (61.3% versus 45.5%, $P < .0001$) than nonattempters. The results suggest that depression with suicidal behavior is a more severe form of illness that requires more aggressive treatment, and they support observations that suicidal behavior is often repeated until it is successful.

Among mood disorders, the risk of suicide is highest in bipolar illness [11]. Patients with mixed states (coexisting manic and depressive symptoms) are at particular risk because of the combination of suicidal thoughts and high levels of energy and impulsivity. For this reason, manic patients are also at high risk of suicide. A family history of suicide doubles the risk of suicide attempts in this and probably in other populations [12].

It is estimated that 5% to 13% of schizophrenia patients commit suicide [13]. A Spanish study of 83 patients with first-episode psychosis found that 14.5% made a suicide attempt and 2.4% committed suicide over the 5 years following the initial hospitalization [14]. Depressive symptoms accompanying psychosis predicted later suicide, and abuse of cocaine and amphetamines increased the risk of suicide eightfold. Suicide attempts in schizophrenia are more likely to be lethal and violent [13]. The introduction of neuroleptics as treatments for schizophrenia did not seem to lower the suicide risk from the era before medications were available [15].

Substance abuse, either as a primary disorder or a condition that is comorbid with other psychiatric disorders, increases the risk of attempted and completed suicide [7,8]. In a cohort of heroin abusers (N = 387), nearly 12% attempted suicide over the 3-year follow-up period [16]. Those with a history of a previous suicide attempt were at increased risk (five times) of another attempt. One fourth of those with suicidal ideation at study enrollment (ie, baseline) made an actual attempt over the next 3 years. Alcohol is involved in 25% to 35 % of all suicides [17,18]. Furthermore, the risk for suicide associated with alcohol dependence increases with age [19]. Similarly, Preuss and colleagues [20], in a cohort of patients (N = 371) with a history of suicidal attempts, found a greater incidence of suicidal attempts among patients with depression and alcohol abuse (61%) compared with those suffering from depression alone (39%). Compared with nondrinking teenagers, adolescents who use alcohol, especially if they began drinking in their preteenage years, had almost a threefold increased risk of suicide attempts [21]. Alcohol use is associated with more dangerous attempts. For example, a review of 406 self-inflicted gunshot wounds to the head found alcohol in the blood of 40% of cases [22].

Because alcohol is the most frequently used and readily available substance, it is a common factor in suicide attempts. There are several reasons why alcohol use increases the risk of suicide attempts and completed suicide [23]. Alcohol not only reduces impulse control, but it provides a potentially fatal substance on which to overdose. Alcohol directly causes depression, and alcoholism is often comorbid with mood disorders. A family history of alcoholism also increases the risk of suicidality, possibly because alcoholic families are more likely to abuse their children (childhood abuse is a risk factor for suicide), and possibly because of familial clustering of alcoholism, depression, and suicide. It is important to evaluate patients who have made a suicide attempt for the presence of alcohol and for alcoholism.

Suicidality in children and adolescents

Suicidal ideation in children is a serious symptom, with a strong association with childhood depression and bipolar illness [24]. In a Dutch study, childhood ($\leq$11 years) suicidal ideation (reported by parents) persisted into adulthood (odds ratio, 10.7) and predicted a lifetime history of suicide attempts (odds ratio, 5.8) [24]. Children with suicidal thoughts had an increased risk of developing a mood or anxiety disorder in adulthood. Suicidal ideation that starts in preadolescence predicts later negative outcomes more strongly than adolescent onset suicidal thoughts. Adolescent suicidality, however, still predicts adult suicide attempts, depression, anxiety, and substance abuse. Suicidal ideation in childhood should not be dismissed as a passing phase.

Suicide is the third leading cause of death in adolescents [8], and 3% of adolescents make medically serious suicide attempts [25]. Suicide rates per 100,000 for children aged 5 to 14 are 0.6 in the United States, 0.5 in the Netherlands, and 0.1 in the United Kingdom; for individuals aged 15 to 24, rates increase to 9.9, 5, and 5.2, respectively [24]. In 2003, there were 3988 reported suicides among people 15 to 24 years old in the United States, with 1487 occurring among those 15 to 19 years old [8]. From 1950 to 1990, the suicide rate for adolescents 15 to 19 years old increased by 300% [26], although it decreased by 35% between 1990 and 2003 [27]. The ratio of attempted to completed suicide in adolescents is 50 to 100:1 [8,28–30]. A 2003 survey of students in grades 9 to 12 in the United States found that 16.5% of students had planned a suicide attempt, 8.5% had made a suicide attempt, and 2.9% had made an attempt that required medical intervention [31].

A mother's report of depression in a child is usually accurate; however, mothers are frequently unaware of suicidal thoughts in their adolescent children, with such thoughts being reported much more frequently by the adolescents themselves than the parents [32]. Risk factors for adolescent suicide include family history of suicide, past history of an attempt, living outside the home, homosexual or bisexual orientation, and history of abuse. Firearms in the home, even if they are locked, are associated with an increased risk of adolescent suicide.

In June 2003, the Food and Drug Administration (FDA) recommended that paroxetine not be used in juvenile patients because of an increased risk of suicide. In October 2004, a black box warning was added to all antidepressants package inserts [33,34]. The FDA black box warning was prompted by analysis of aggregate data from 24 clinical trials that found a doubling in suicidality (defined as new-onset or increased suicidal thinking or new suicide attempts) among pediatric patients on active drug (4%) compared with placebo (2%). The data on which the FDA based their advisory were extracted from 24 trials (23 trials conducted in nine drug company–supported programs evaluating the effectiveness of antidepressants in

pediatric patients and one National Institutes of Mental Health–sponsored multicenter trial [the TADS trial]) lasting 4 to 16 weeks and involving 4582 children and adolescents. The antidepressants involved included fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone, and mirtazepine. The trials were intended to assess the effectiveness of the medications in the treatment of major depression (16 trials); obsessive-compulsive disorder (4 trials); generalized anxiety disorder (2 trials); and social anxiety disorder (1 trial). Analysis of the data revealed there were 89 cases of suicidal behavior or ideation and 120 cases of possible suicidal behavior or ideation. In addition, 11 cases were classified as self-injury with nonsuicidal intent and an additional 47 events occurred in 21 patients who had more than one event. Of note, no completed suicides occurred in any of the trials [35].

It is important to bear in mind that none of the pediatric studies was designed to evaluate suicide risk; the data were obtained only from events that researchers happened to notice or report; the studies had different designs and durations and in general were too short adequately to evaluate risks in actual clinical practice; and multiple statistical tests were performed, increasing the likelihood of a spurious result [35]. It is also possible that placebo patients dropped out of studies sooner than patients in active treatment because of lack of benefit, and before they exhibited suicidality, artificially elevating the apparent risk in patients given antidepressants. Given that early onset depression is associated with an increased likelihood of a bipolar disorder, it is possible that some cases of bipolar mood disorders were missed in the initial evaluations and the condition was exacerbated by antidepressants, leading to increased agitation and impulsivity. Rates of suicidality were found to decrease in patients on active antidepressant therapy [8]. Furthermore, a reanalysis of data including seven more studies and a more conservative statistical model found only a 0.7% greater incidence of suicidality with active drug versus placebo [8]. Only the National Institutes of Mental Health–sponsored TADS trial reported statistically significantly increased suicidality in subjects taking antidepressants versus placebo. For these patients, it may be that increased energy or comfort with the clinician made it easier to reveal thoughts that were concealed previously, something that was less likely to occur with placebo [36]. The fact that no suicides occurred is not entirely reassuring, however, in a relatively small sample. The FDA warning that juvenile patients taking antidepressants be evaluated and followed carefully makes clinical sense. Similarly, there is no reason to deny the use of antidepressants in adolescents in need when administered by competent clinicians.

The warning by the FDA had a distinct impact on prescribing practices. Before the FDA's first public health advisory, there had been a 36% per year increase in antidepressant prescriptions for youth aged 6 to 17. Similarly, from 1985 to 1999 there was a fourfold increase in per capita

antidepressant prescriptions for this population [37]. Following the 2004 warning, antidepressant prescriptions for this population decreased by 0.8% per year, with paroxetine use in juvenile patients decreasing by 44%. After the FDA's second warning prescriptions decreased by 10% per year. Antidepressant prescriptions for adults also decreased, although to a lesser degree during this period, whereas antidepressant prescriptions for the elderly increased by 8%.

Did the decrease in antidepressant prescriptions for children and adolescents improve treatment and reduce suicide rates in this population? Between 1950 and 1990, before antidepressants were widely prescribed for juvenile patients, the rate of adolescent suicide had increased by 300%. Between 1990 and 2003, however, suicide rates decreased by 35% in association with an increase in antidepressant prescriptions. Then, from 2003 to 2004, after the black box warning was introduced and antidepressant prescriptions for children declined, the suicide rate increased by 18% [8]. Similarly, a claims database study involving 65,349 newly diagnosed cases of pediatric depression found that between 1999 and 2004, the rate of diagnosis of depression in this population increased from 3 per 1000 to 5 per 1000. Following the FDA advisory, the rate decreased back to pre-1999 levels, primarily as a function of decreased diagnosis of pediatric depression by pediatricians and family physicians [38]. Before the FDA 2004 advisory, 59% of depressed children received a prescription for a selective serotonin reuptake inhibitor. The trend toward increasing selective serotonin reuptake inhibitor prescriptions was reversed after the advisory such that only 28% of depressive episodes were treated with a selective serotonin reuptake inhibitor [38]. The reduction in antidepressant prescribing was not matched by an increase in nonpharmacologic therapies. A study comparing adolescent suicide rates in 588 zip code zones found a 0.23 per 100,000 decrease in adolescent suicide for every 1% increase in antidepressant prescriptions [37]. Of note, if suicidal thinking in adolescents does increase after starting an antidepressant, it usually occurs within the first month of treatment and most frequently within the first 7 to 10 days [36].

In addition to the decrease in the diagnosis and treatment of childhood depression after the FDA advisory, there was a halo effect on the diagnosis and treatment of adult depression. An analysis of managed care claims from 1998 to 2005 involving 475,838 different depressive episodes found that the percentage of depressed adults who did not receive an antidepressant increased from 20% to 30% after the FDA warning, without any parallel increase in the use of other medications or psychotherapy [39]. In adults and children, the FDA recommendation that depressed patients be seen seven times in the first 3 months of treatment was adhered to less than 5% of the time, and the frequency of monitoring did not increase after the warning [40]. Only 60% of children and 40% of adults were seen three times in the first 3 months of treatment (a more liberal guideline) both before and after the FDA warning [40].

Neurobiology of suicide

The most robust neurobiologic finding in suicide has involved multiple dimensions of serotonergic dysfunction, including reduced central serotonin turnover and a polymorphism of the serotonin transporter [41,42]. The association of serotonergic dysfunction is particularly strong for violent and impulsive suicide, but it is not specific to any diagnosis. Similar findings have been reported for other forms of violent and impulsive behavior, such as firesetting [43]. The association is understandable in that serotonin modulates impulsivity and aggression, whether it is directed outward or toward the self [44].

In the STAR*D study, patients in 18 primary care and 23 psychiatry centers (N = 1879) began treatment with citalopram. Of these, 124 (9%) developed new-onset suicidal thoughts after starting the antidepressant. Among the men in the study, two single nucleotide polymorphisms that flanked the transcription factor cyclic AMP response binding element protein gene (CREB1) were significantly associated with treatment-emergent suicidal thoughts [45]. In a previous study conducted by these investigators the same single nucleotide polymorphisms were associated with difficulty with anger expression in depressed men [45]. No neurobiologic finding has yet proved useful for predicting suicide risk.

Outcome following a suicide attempt

Following a suicide attempt, the risk of another attempt is 12% to 30% and the risk of completed suicide in the next year is 1% to 3% [46]. In a study of 1573 attempted suicides evaluated in the psychiatric emergency room of the Karolinska Hospital between 1981 and 1988, 11% died and 6% committed suicide over an average of 5 years of follow-up [47]. The risk of successful suicide after an attempt was 8.3% for men and 4.3% for women and was greatest during the first year following an attempt. In a study involving 925 patients admitted to psychiatric units following a suicide attempt, expression of a wish to die was the best predictor of later successful suicide [48].

A 12-month study conducted in the north of France [46] followed 605 adult patients who were discharged from the emergency department after having been evaluated by a psychiatrist following a suicide attempt by overdose. Patients were randomized to one of three groups: (1) telephone contact 1 month after discharge; (2) telephone contact at 3 months after discharge; or (3) usual care (ie, no contact, which constituted the control group). The principle of contacting participants was to go back over the treatment recommended in the emergency department: if treatment was difficult to follow a new one was suggested, or if patients were considered at high risk of suicide an urgent appointment was made at the emergency department in which they had originally been treated. The psychotherapeutic approach used was psychologic support. The

experimental intervention included an attempt to enhance compliance with treatment and to provide brief crisis intervention when needed. Of the 107 participants contacted at 1 month, 72 were ordinary calls (lasting 5–10 minutes); 22 concerned crisis intervention (15–45 minutes); and 13 detected participants at high risk of suicide. Seven of the 72 participants who seemed alright at the time of contact attempted suicide during the following year. Of the 22 participants who required crisis intervention, 5 attempted suicide within a year. Thirteen participants were sent to the emergency department; 10 were considered by the psychiatrist as being at risk and 8 of these were admitted to hospital. Only 1 of these 13 patients reattempted suicide, 6 months later. The authors conclude that contacting patients a month after an overdose has the potential to reduce further attempts and identify those at immediate risk.

Predicting suicide and suicide attempts

A substantial number of individuals who die by suicide see their primary care physician shortly before their death [7,8,49], most within 1 month of dying [4]. Yet, physicians have not been very effective at recognizing and preventing its occurrence. Several studies have demonstrated that patients who commit suicide by overdose often obtain the medication of the agent used in the attempt from their primary care physician.

Feldman and associates [4] conducted a study to assess physician characteristics associated with exploring suicidality in patients with depressive symptoms and whether a patient's request of antidepressant influenced physician's behavior. The study used standardized patients portraying two conditions (ie, major depression and adjustment disorder) who made unannounced visits to 152 primary care physicians. The study revealed that suicide was explored in only 36% of 298 encounters. Exploration of suicidality was more common when the patient portrayed major depression (versus adjustment disorder; $P = .03$); when subjects requested an antidepressant (versus no request; $P = .02$); in academic settings ($P < .01$); and among physicians with personal experience with depression ($P < .01$).

The intervention consisted of a depression screening of randomly sampled patients. It showed a decrease in rates of suicidal ideation from 29% to 17% in the intervention group as expected; patients in the intervention group had a more favorable course of depression in both degree and speed of symptom reduction [49]. It is not true that patients who talk about suicide do not go on to kill themselves. Patients who communicate suicidal intention should always be taken seriously, especially in an acute care setting.

Some demographic risk factors for suicide that have been reported in population studies, including male gender, older age, unmarried, unemployed, and recent loss, are not particularly helpful in an individual patient. Careful application of general risk factors may not predict exactly who will

commit suicide. For example, a Danish population registry study found that the risk of suicide was higher in patients with a psychiatric history who were employed and married [50]. Hopelessness, however, is a consistent predictor of suicide risk [51]. One study showed that all-or-nothing thinking that creates the belief that if a problem cannot be solved perfectly it cannot be solved at all, leading to hopelessness when one's efforts are not completely successful, predicted later suicide attempts and suicide [52,53]. In adolescent girls, a history of date rape increases the risk of a suicide attempt [52].

A history of violence against others predicts violence against the self. A follow-up study of 550 patients who had been in a secure psychiatric setting because of violent behavior found that 3.2% eventually committed suicide, a rate more than 300 times higher than in the general population [54]. In the United States, about 4% of people who kill someone else go on to commit suicide. Occasionally, a depressed patient commits "suicide by police" by engaging in a violent confrontation with strangers, but most violence by suicidal people involves domestic partners, with most murderers being men. The risk that a man who has made a suicide attempt may go on to kill a partner is increased by a history of domestic violence in the relationship and the presence of firearms in the home [55]. All patients who have made a suicide attempt should be evaluated for a risk of violence to others, and vice versa.

Nonsuicidal self-injurious behavior, such as cutting, burning, hitting, or less frequently biting or abrading parts of the body in ways that may be obvious or covert, is usually associated with personality disorders. In these cases, it serves as a mechanism for expiating guilt, creating a concrete physical sensation that distracts from mental disorganization, or manipulative behavior. Nonsuicidal self-injurious behavior is not uncommon, however, in depression and psychosis. Although patients usually do not intend nonsuicidal self-injurious behavior itself to have a fatal outcome, the occurrence increases the risk of subsequent actual suicide attempts sixfold [56]. Patients treated for nonsuicidal self-injurious behavior should be evaluated for suicidal intention.

Given that suicide is a rare event (average rate in American adults 11 per 100,000), it is impossible to design a prospective study of absolute predictive factors that involves fewer than 1 million subjects [57]. Although it remains impossible to predict suicide precisely, it is possible to assess risk in a clinically relevant manner [58,59]. Suicide risk assessment, which is not only possible but clinically necessary, is not the same as suicide prediction. In addition to hopelessness, the presence of a plan, especially if the patient has the means to carry it out, greatly increases suicide risk. The risk is even higher if the patient has practiced the plan (eg, by taking a few extra pills) and the patient cannot think of any reason not to die. Psychosis, especially if it includes hallucinated voices telling the patient to commit suicide (command hallucinations), increases the risk even further. In hospitalized patients with painful injuries or medical illnesses, the severity of pain at discharge predicts the persistence of significant suicidal ideation [60].

Some clinicians believe that suicidal patients who endorse a ''no-suicide contract'' and promise not to kill themselves are at decreased risk. There is no empiric support at all, however, for this approach [61]. Patients with the features just outlined who cannot give a cogent reason why they would not act on suicidal thoughts beyond a promise to the clinician should still be considered to be suicidal.

Treatment

Suicide prevention centers are relied on in some communities as a first-line treatment for suicidal individuals. Data over the past 30 years indicate, however, that callers to these centers generally do not present a high risk [62] and that the centers have not had a significant impact on local suicide rates [63,64]. Clinically meaningful detection and treatment of suicide risk occurs most frequently in the primary care setting and in the emergency department. The Centers for Disease Control and Prevention has published lists of risk factors and protective factors for suicide (Boxes 1 and 2) [65], although these are based on population studies and are not always predictive in the individual patient. When the risk of suicide is high, or when the

Box 1. Risk factors for suicide

- Family history of suicide
- Family history of child maltreatment
- Previous suicide attempts
- History of mental disorders, particularly depression
- History of alcohol and substance abuse
- Feelings of hopelessness
- Impulsive or aggressive tendencies
- Cultural and religious beliefs (eg, belief that suicide is noble resolution of a personal dilemma)
- Local epidemics of suicide
- Isolation, a feeling of being cut off from other people
- Barriers to accessing mental health treatment
- Loss (relational, social, work, or financial)
- Physical illness
- Easy access to lethal methods
- Unwillingness to seek help because of the stigma attached to mental health and substance abuse disorders or to suicidal thoughts

Data from US Public Health Service 1999. Available at: http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm. Accessed April 1, 2008.

Box 2. Protective factors for suicide

- Effective clinical care for mental, physical, and substance abuse disorders
- Easy access to a variety of clinical interventions and support for help seeking
- Family and community support
- Support from ongoing medical and mental health care relationships
- Skills in problem solving, conflict resolution, and nonviolent way of handling disputes
- Cultural and religious beliefs that discourage suicide and support instincts for self-preservation

Data from US Public Health Service 1999. Available at: http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm. Accessed April 1, 2008.

patient refuses to divulge enough information to assess risk, the most prudent approach is to hospitalize the patient to a psychiatric ward. One must keep in mind that 15% of suicides occur after a patient has refused voluntary hospitalization [66]. The most immediate concern is actively preventing the patient from acting on suicidal intention. Although patients may ruminate about suicide for years, the acute risk lasts only hours to days. Physically containing the patient until the acute impulse abates is the cornerstone of suicide prevention in the short-term. Close observation may be necessary, because attempts and even successful suicide have been known to occur in the hospital. The period of highest risk after discharge from the hospital is the first 2 to 4 weeks postdischarge [66].

In the longer-term, almost any form of treatment that engages the patient in a constructive relationship can reduce the risk of suicide [67]. Dialectical behavior therapy (DBT), however, a specialized form of cognitive psychotherapy usually conducted in a group setting, has been shown to reduce suicidal and self-injurious behavior and the tendency to drop out of treatment in patients with personality disorders [68]. Although there is less research on DBT for mood disorders, there is reason to believe that it may also be effective for self-injurious behavior in major depression. A total of 101 clinically referred women with recent suicidal and self-injurious behaviors were randomized to 1 year of DBT or 1 year of community treatment by experts. DBT was associated with better outcomes in the intent-to-treat analysis than community treatment by experts in most target areas during the 2-year treatment and follow-up period. Subjects receiving DBT were half as likely to make a suicide attempt (hazard ratio, 2.66; $P = .005$), required less hospitalization for suicide ideation ($F[1,92] = 7.3$; $P = .004$), and had

lower medical risk (F[1,50] = 3.2; $P = .04$) across all suicide attempts and self-injurious acts combined. Subjects receiving DBT were less likely to drop out of treatment (hazard ratio, 3.2; $P < .001$) and had fewer psychiatric hospitalizations (F[1,92] = 6; $P = .007$) and psychiatric emergency department visits (F[1,92] = 2.9; $P = .04$) [69].

A study of patients with borderline personality disorder (N = 20) treated with a 6-month course of DBT found significant reductions in nonsuicidal self-injury urges, nonsuicidal self-injury, suicide ideation, subjective distress, depression, and hopelessness between baseline and 6 months. The authors concluded that the use of DBT in a 6-month treatment format may be sufficient to target suicidal behavior and ideation [17–20,70–72].

Because suicidality is usually a symptom of a major psychiatric illness, effective treatment of the primary disorder usually eliminates the risk of suicide. Relapse and recurrence are common in both mood and psychotic disorders, however, so ongoing treatment and monitoring is necessary. Somatic therapies (medications and electroconvulsive therapy) are selected based on the features of the specific psychiatric disorder. When selecting antidepressant agents, consider the fact that tricyclic antidepressants are more dangerous in overdose than the selective serotonin reuptake inhibitors. Only lithium [73] and clozapine have been shown to reduce suicide risk independent of their effect on the primary disorder, the latter by more than 80% in one study [15].

Management in the critical care setting

The goals of treatment for patients who are in a critical care setting because they have made a suicide attempt are to keep the patient safe, treat the injuries, assess ongoing suicide risk, and begin or arrange definitive psychiatric therapy. Many overdoses involve alcohol and other central nervous system depressants, such as tranquilizers and sleeping pills, and these substances are often ingested before violent suicide attempts. Early toxicology screening, and a history obtained promptly from significant others and the patient can identify patients at risk of withdrawal syndromes and can clarify the cause of continued confusion or agitation. Substance withdrawal should be suspected whenever any acute unexplained change in behavior or mental status occurs in a patient who is hospitalized after a suicide attempt after an initial period of apparent stability. In this case, however, blood levels are likely to be zero. Withdrawal from any combination of central nervous system depressants can be diagnosed by challenge with phenobarbital or pentobarbital [74]. Similarly, acute changes in mental status could also represent an overdose taking place in the hospital setting, as in the case of patients who ingest medications brought into the hospital during admission.

Many patients feel temporarily better after a suicide attempt because the escalating dysphoria that led to the attempt has decreased. This does not mean, however, that the patient is safe. It is necessary to assess the ongoing

risk of suicide or gross noncompliance with medical or surgical therapy. Patients who openly express disappointment at having survived are at particularly increased risk, especially if they continue to express a wish to die or to leave the hospital immediately. Patients who made an obvious suicide attempt but deny that they were trying to kill themselves, and patients who say that they would never repeat the attempt but who cannot describe any coherent reason why they would have changed their minds, are also at high risk. Also at high risk are patients with ongoing confusion or psychosis, patients who made a violent or very dangerous attempt with little chance of rescue, and those with no available support system. Conversely, if a suicide attempt has solved a problem temporarily (eg, by convincing a spouse not to leave or by mobilizing family support), the risk during the acute hospital stay is lower.

Patients at high risk of suicide while in a nonpsychiatric setting need continued close observation. If a sitter is used, the sitter should have experience working with psychiatric patients. Patients who actively resist treatment or try to leave the hospital are best treated on inpatient units that can provide both medical and psychiatric care, but if such a unit is not available, chemical or physical restraint may be necessary. The use of emergency tranquilization is a complicated issue, but controlled studies of antipsychotic drugs with or without benzodiazepines or antihistamines have only been performed in the emergency department and recommendations have to be extrapolated to the inpatient setting. The American College of Emergency Physicians, after an extensive literature review, found no class I studies of the emergency treatment of nonpsychotic agitation [75]. The safest and most rapidly effective approach is probably with intramuscular benzodiazepines, such as midazolam [75]. Atypical antipsychotic drugs are often used for nonpsychotic agitation but the evidence of their efficacy is not strong [76,77]. Agitation in psychotic patients can be treated effectively with antipsychotic drugs.

There are multiple potential means of suicide in the hospital that should be addressed for patients with ongoing suicidal intention. Such patients should not be in a bed near a window, even if the glass is unbreakable, because they attempt to jump through it if they do not know this is not possible. Blocking electrical outlets that the patient can reach easily and minimizing access to means of strangulation may be necessary. Most critical care units are not as ''suicide proof'' as psychiatric units (eg, breakaway shower heads and sloping doors to prevent hanging), necessitating close observation until transfer is possible. When the patient is to remain on a nonpsychiatric service, the psychiatric consultant should see the patient daily.

All states have provisions for involuntary hospitalization and treatment of patients who present a danger to themselves or others or who are gravely disabled or disorganized. These laws usually involve certification by one or more physicians of the need for hospitalization. Permission for involuntary administration of medications in patients who are refusing treatment may have to be obtained separately from permission to keep the patient in the

hospital. The psychiatric consultant can assist with these interventions, which may require a physician to petition the court in person if a judge does not come to the hospital for such proceedings.

When patients need prolonged care in a critical care setting, as may occur with multiple severe injuries, treatment of the underlying psychiatric disorder should be instituted by the psychiatric consultant. It is very important to consider potential interactions between psychiatric medications and other medicines the patient may be taking. Whereas psychosis can be reduced fairly rapidly with antipsychotic drugs, antidepressants take a month or more to be effective. Patients who are severely depressed should be considered candidates for electroconvulsive therapy, which is rapidly effective and has fewer interactions than antidepressants. The only contraindications to electroconvulsive therapy are space-occupying lesion and recent myocardial infarction [66].

On rare occasions, such injuries as esophageal damage from ingestion of lye or a gunshot or stab wound may interfere with the use of oral medications. Agitation can be treated with parenteral benzodiazepines, such as midazolam or lorazepam, but there are no clinically practical parenteral antidepressants. If it is not possible to administer medications by a feeding tube, parenteral benzodiazepines may at least reduce distress and improve sleep until an antidepressant can be administered.

Summary

The risk of completed suicide is high in patients treated in a critical care setting for a suicide attempt, especially if the attempt had high risk (eg, shooting, hanging, large overdose) and a low chance of rescue. One should keep in mind that some patients practice suicide with a mild attempt that may seem to be just a gesture. Severe depression, psychosis, substance abuse, hopelessness, expression of regret at being saved, a continued desire to die, or a family history of suicide substantially increase the risk of suicide in the near future. The lack of prospective data predicting exactly who will eventually carry out a plan after expressing suicidal thoughts or making a suicide attempt should in no way impede clinicians from asking patients about a plan, the means to carry out the plan, and factors that might prevent the patient from acting on the plan. Early transfer to a psychiatric unit is desirable, but if continued treatment in the critical care setting is necessary, collaboration with the consulting psychiatrist can reduce the ongoing immediate suicide risk and manage agitation and nonadherence.

References

[1] Claassen CA, Trivedi MH, Rush AJ, et al. Clinical differences among depressed patients with and without a history of suicide attempts: findings from the STAR*D trial. J Affect Disord 2007;97:77–84.

[2] Bossuyt N, Van Casteren V. Epidemiology of suicide and suicide attempts in Belgium: results from the sentinel network of general practitioners. Int J Public Health 2007;52:153–7.
[3] Reseland S, Le Nourv J, Aldred G, et al. National suicide rates 1961–2003: further analysis of Nordic data for suicide, autopsies, and ill-defined death rates. Psychother Psychosom 2008; 77:78–82.
[4] Feldman MD, Franks P, Duberstein PR, et al. Let's not talk about it: suicide inquiry in primary care. Ann Fam Med 2007;5:412–8.
[5] Mattisson C, Bogren M, Horstmann V, et al. The long-term course of depressive disorders in the Lundby study. Psychol Med 2007;37:883–91.
[6] Lonnqvist JK, Henriksson MM, Isometsa ET, et al. Mental disorders and suicide prevention. Psychiatry Clin Neurosci 1995;49(Suppl 1):S111–6.
[7] Szanto K, Kalmar S, Hendin H, et al. A suicide prevention program in a region with a very high suicide rate. Arch Gen Psychiatry 2007;64:914–20.
[8] Shain BN. Suicide and suicide attempts in adolescents. Pediatrics 2007;120:669–76.
[9] Foley PL, Goldston DB, Costello EJ, et al. Proximal psychiatric risk factors for suicidality in youth: the Great Smoky Mountains Study. Arch Gen Psychiatry 2006;63:1017–24.
[10] Gaynes BN, Rush AJ, Trivedi MH, et al. Major depression symptoms in primary care and psychiatric care settings: a cross-sectional analysis. Ann Fam Med 2007;5:126–34.
[11] Goodwin FK, Jamison KR. Manic depressive illness. New York: Oxford University Press; 1991.
[12] Romero S, Colom FI, Losif AM, et al. Relevance of family history of suicide in the long-term outcome of bipolar disorders. J Clin Psychiatry 2007;68:1517–21.
[13] Altamuraa AC, Bobob WV, Meltzer HY. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. Int Clin Psychopharmacol 2007;22:249–67.
[14] Gonzalez-Pinto A, Aldama A, Gonzalez C, et al. Predictors of suicide in first-episode affective and nonaffective psychotic inpatients: five-year follow-up of patients from a catchment area in Vitoria. Spain. J Clin Psychiatry 2007;68:242–7.
[15] Meltzer HY, Alphs L, Green Al, et al. Clozapine treatment for suicidality in schizophrenia. International Suicide Prevention Trial. Arch Gen Psychiatry 2003;60:82–91.
[16] Darke S, Ross J, Williamson A, et al. Patterns and correlates of attempted suicide by heroin users over a 3-year period: findings from the Australian treatment outcome study. Drug Alcohol Depend 2007;87:146–52.
[17] Cherpitel CJ, Bond J, Ye Y, et al. A cross-national meta-analysis of alcohol and injury: data from the Emergency Room Collaborative Alcohol Analysis Project (ERCAAP). Addiction 2003;98:1277–86.
[18] Kelly C, Galloway R. Deliberate self-poisoning presenting at Craigavon area hospital: 1976 and 1986. Ulster Med J 1992;61:12–8.
[19] Conner KR, Beautrais AL, Conwell Y. Moderators of the relationship between alcohol dependence and suicide and medically serious suicide attempts: analyses of Canterbury Suicide Project data. Alcohol Clin Exp Res 2003;27:1156–71.
[20] Preuss UW, Schuckit MA, Smith TL, et al. A comparison of alcohol-induced and independent depression in alcoholics with histories of suicide attempts. J Stud Alcohol 2002;63: 498–502.
[21] Swahn MH, Bossarte RM. Gender, early alcohol use, and suicide ideation and attempts: findings from the 2005 youth risk behavior survey. J Adolesc Health 2007;41:175–81.
[22] Blumenthal R. Suicidal gunshot wounds to the head: a retrospective review of 406 cases. Am J Forensic Med Pathol 2007;28:288–91.
[23] Makhija N, Sher L. Childhood abuse, adult alcohol use disorders and suicidal behaviour. QJM 2007;100:305–9.
[24] Herba CM, Ferdinand RF, Van der Ende J, et al. Long-term associations of childhood suicide ideation. J Am Acad Child Adolesc Psychiatry 2007;46:1473–81.
[25] Spirito A, Esposito-Smythers C. Attempted and completed suicide in adolescence. Annu Rev Clin Psychol 2006;2:237–66.

[26] O'Carroll PW, Potter LB, Mercy JA. Programs for the prevention of suicide among adolescents and young adults. MMWR Recomm Rep 1994;43(RR-6):1–7.
[27] Prevention CfDCa: CDC Wonder [database]: mortality query. Available at: http://wonder.cdc.gov.2006. Accessed April 25, 2008.
[28] Husain SA. Current perspective on the role of psychological factors in adolescent suicide. Psychiatr Ann 1990;20:122–7.
[29] Centers for Disease Control and Prevention. Youth risk behavior surveillance—United States, 2003. MMWR Surveill Summ 2004;53(2):1–96. Available at: www.cdc.gov/mmwr/PDF/SS/SS5302.pdf. Accessed April 25, 2008.
[30] Centers for Disease Control and Prevention. Suicide prevention scientific information: risk and protective factors—United States 1999. Available at: http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm. Accessed April 21, 2008.
[31] Centers for Disease Control. Prevention CfDCa: youth risk behavior surveillance—United States, 2003. MMWR Morb Mortal Wkly Rep 2004;53:536.
[32] Rice F, Lifford KJ, Thomas HV, et al. Mental health and functional outcomes of maternal and adolescent reports of adolescent depressive symptoms. J Am Acad Child Adolesc Psychiatry 2007;46:1162–70.
[33] Administration USFaD: PDA public health advisory: suicidality in children and adolescents being treated with antidepressant medications. Available at: http://www.fda.gov/cder/drug/antidepressants/SSRIPHA20041Q.htm, 2006: www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. Accessed April 25, 2008.
[34] Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry 2008;65:94–101.
[35] Hammad TA, Langhren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–9.
[36] Emslie GJ, Waslick B, Weller EB, et al. Antidepressant management in the context of suicidal ideation. J Am Acad Child Adolesc Psychiatry 2007;46:1222–5.
[37] Olfson M, Shaffer D, Marcus SC, et al. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 2003;60:978–82.
[38] Libby AM, Brent DA, Morrato EH, et al. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007;164:884–91.
[39] Valuck RJ, Libby AM, Orton HP, et al. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2007;164:1198–205.
[40] Morrato EH, Libby AM, Orton HP, et al. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry 2008;165:42–50.
[41] Banki CM. Prophylactic potential of selective reuptake inhibitors in suicidal patients. Int Clin Psychopharmacol 1995;9(Suppl 4):61–5.
[42] Bellivier F, Szoke A, Henry C, et al. Possible association between serotonin transporter gene polymorphism and violent suicidal behavior in mood disorders. Biol Psychiatry 2000;48:319–22.
[43] Linnoila M, Virkkunen M. Biologic correlates of suicidal risk and aggressive behavioral traits. J Clin Psychopharmacol 1992;12:19S–20S.
[44] Dubovsky SL, Thomas M. Beyond specificity: effects of serotonin and serotonergic treatments on psychobiological dysfunction. J Psychosom Res 1995;39(4):429–44.
[45] Perlis RH, Purcell S, Fava M, et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. Arch Gen Psychiatry 2007;64:689–97.
[46] Vaiva G, Ducrocq F, Meyer P, et al. Effect of telephone contact on further suicide attempts in patients discharged from an emergency department: randomised controlled study. BMJ 2006;332:1241–6.
[47] Nordstrom P, Samuelsson M, Asberg M. Survival analysis of suicide risk after attempted suicide. Acta Psychiatr Scand 1995;91(5):336–40.

[48] Hjelmeland H. Verbally expressed intentions of parasuicide: II. Prediction of fatal and non-fatal repetition. Crisis 1996;17(1):10–4.
[49] Bruce ML, Ten Have TR, Reynolds CF, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA 2004;291:1081–91.
[50] Agerbo E. High income, employment, postgraduate education, and marriage: a suicidal cocktail among psychiatric patients. Arch Gen Psychiatry 2007;64:1377–84.
[51] Beck AT, Weishaar ME. Suicide risk assessment and prediction. Crisis 1990;11(2):22–30.
[52] Hughes SL, Neimeyer RA. Cognitive predictors of suicide risk among hospitalized psychiatric patients: a prospective study. Special issue: prevention and postvention of suicide. Death Stud 1993;17(2):103–24.
[53] Olshen E, McVeigh KH, Wunsch-Hitzig RA, et al. Dating violence, sexual assault, and suicide attempts among urban teenagers. Arch Pediatr Adolesc Med 2007;161:539–45.
[54] Davies S, Clarke M, Hollin C, et al. Long-term outcomes after discharge from medium secure care: a cause for concern. Br J Psychiatry 2007;191:70–4.
[55] Salari S. Patterns of intimate partner homicide suicide in later life: strategies for prevention. Clin Interv Aging 2007;2:441–52.
[56] Whitlock J, Knox KL. The relationship between self-injurious behavior and suicide in a young adult population. Arch Pediatr Adolesc Med 2007;161:634–40.
[57] Khan A, Schwartz K. Suicide risk and symptom reduction in patients assigned to placebo in duloxetine and escitalopram clinical trials: analysis of the PDA summary basis of approval reports. Ann Clin Psychiatry 2007;19:31–6.
[58] Cantor CH, McDermott PM. Suicide litigation: from legal to clinical wisdom. Aust N Z J Psychiatry 1994;28(3):431–7.
[59] Goldstein RB, Black DW, Nasrallah A, et al. The prediction of suicide: sensitivity, specificity, and predictive value of a multivariate model applied to suicide among 1906 patients with affective disorders. Arch Gen Psychiatry 1991;48(5):418–22.
[60] Edwards RR, Magyar-Russell G, Thombs B, et al. Acute pain at discharge from hospitalization is a prospective predictor of long-term suicidal ideation after burn injury. Arch Phys Med Rehabil 2007;88(12 Suppl 2):S36–42.
[61] Rudd MD, Mandmsiak M, Joiner TE Jr. The case against no-suicide contracts: the commitment to treatment statement as a practice alternative. J Clin Psychol 2006;62: 243–51.
[62] de Anda D, Smith MA. Differences among adolescent, young adult, and adult callers of suicide help lines. Soc Work 1993;38:421–8.
[63] Bridge TP, Potkin SG, Zung WW, et al. Suicide prevention centers: ecological study of effectiveness. J Nerv Ment Dis 1977;164:18–24.
[64] Kutcher SP, Szumilas M. Youth suicide prevention. CMAJ 2008;178:282–5.
[65] Prevention CfDCa: Suicide prevention scientific information: risk and protective factors United States 1999. Available at: http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm. 1999; http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm. Accessed April 25, 2008.
[66] Dubovsky SL, Weissberg MP. Clinical psychiatry in primary care. 3rd edition. Baltimore (MD): Williams and Wilkins; 1986.
[67] Cosgrave EM, Robinson J, Godfrey KA, et al. Outcome of suicidal ideation and behavior in a young, help-seeking population over a 2-year period. Crisis 2007;28:4–10.
[68] Clarkin JF, Levy KN, Lenzenweger MF, et al. Evaluating three treatments For borderline personality disorder: a multiwave study. Am J Psychiatry 2007;164:922–8.
[69] Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry 2006;63(7):757–66.
[70] Stanley B, Brodsky B, Nelson JD, et al. Brief dialectical behavior therapy (DBT-B) for suicidal behavior and non-suicidal self injury. Arch Suicide Res 2007;11(4):337–41.

[71] Centers for Disease Control and Prevention. CDC Wonder [database]: mortality query. Available at: http://wonder.cdc.gov. Accessed October 9, 2006.
[72] US Food and Drug Administration. FDA public health advisory: suicidality in children and adolescents being treated with antidepressant medications. Available at: www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. Accessed October 9, 2006.
[73] Muller-Oerlinghausen B, Berghofer A, Ahrens B. The antisuicidal and mortality-reducing effect of lithium prophylaxis: consequences for guidelines in clinical psychiatry. Can J Psychiatry 2003;48:433–9.
[74] Smith D, Wesson PR. Berizodiazepines and other sedative-hypnotics. In: Galanter M, Kleber HP, editors. American psychiatric press textbook of substance abuse treatment. 2nd edition. Washington, DC: American Psychiatric Press; 1999. p. 239–50.
[75] Lukens TW, Wolf SJ, Edlow JA, et al. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. Ann Emerg Med 2006;47:79–99.
[76] Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's. N Engl J Med. 2006;355:1525–38.
[77] Dubovsky SL. Using electroconvulsive therapy for patients with neurological disease. Hosp Community Psychiatry 1986;37:819–25.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 875–887

CRITICAL
CARE
CLINICS

Posttraumatic Stress Disorder Following Critical Illness

Erin K. Kross, MD, Cynthia J. Gries, MD, MSc, J. Randall Curtis, MD, MPH*

Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, School of Medicine, University of Washington, 325 Ninth Avenue, Seattle, WA 98104-2499, USA

Posttraumatic stress disorder (PTSD) is a common psychiatric condition that can occur after a traumatic event. PTSD is the fourth most common psychiatric illness in the United States with estimates of lifetime prevalence ranging from 5% to 6% in men to 10% to 14% in women [1]. Traumatic events can provoke fear, helplessness, or horror in response to an event that threatens life or safety [1]. Prevalence estimates for adults who are at risk for PTSD range from 2% to 15% after combat in Vietnam to 14% to 80% after rape [2]. In addition to PTSD, individuals exposed to traumatic events also are at risk for other psychologic morbidity, such as depression, panic disorder, generalized anxiety disorder, and substance abuse. The burden of PTSD can be high and can result in an inability to work or return to prior levels of functioning. Therefore, PTSD results in an increased cost to society because of increased health care costs and decreased productivity.

The criteria for PTSD are defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) [3]: a person must have been exposed to a traumatic event, which involves a perceived or actual threat to the person's own life or physical integrity or that of another person. The condition is characterized by a constellation of symptoms in three domains: (1) symptoms of re-experiencing, (2) symptoms of avoidance and emotional numbing, and (3) symptoms of increased arousal. These symptoms must meet two criteria to satisfy the diagnosis: (1) symptoms must cause significant impairment in social, occupational, or other important

* Corresponding author. Division of Pulmonary and Critical Care, Harborview Medical Center, University of Washington, 325 Ninth Avenue, Box 359762, Seattle, WA 98104-2499.
E-mail address: jrc@u.washington.edu (J.R. Curtis).

0749-0704/08/$ - see front matter
doi:10.1016/j.ccc.2008.06.002 *criticalcare.theclinics.com*

functional domains and (2) symptoms must be present for a least 1 month after exposure to the traumatic event or events.

ICU treatment for critical illness exposes patients and their families to enormous stress. This stress results from the experience of life-threatening illness and the need for intensive, and often invasive, medical procedures. Survivors of critical illness often report memories of pain and anxiety during their ICU stay [4]. Therefore, the trauma of a critical illness and ICU treatment meets the criteria of a traumatic event as stated by the *DSM-IV* criteria of PTSD. A similar experience applies to family members of critically ill patients, as the *DSM-IV* definition allows for a traumatic, life-threatening event to be witnessed rather than personally experienced. Family members of ICU patients may be at risk for PTSD as ICUs are a foreign and often frightening environment for many family members. Family members may be exposed to invasive monitoring for their loved ones and unfamiliar medical procedures and devices. In addition, family members often are asked to assume the role of surrogate decision maker, because the majority of patients in ICUs are not able to participate in decisions about withholding or withdrawing life support. The role of being a surrogate decision maker seems to be associated with additional stress for some family members [5]. Therefore, three groups are considered that are at risk for PTSD after ICU treatment. First, there are patients who survive a critical illness and are discharged after ICU care. Second, there are family members of individuals who survive critical illness. Finally, there are family members of individuals who die during or shortly after their ICU stay. This article reviews the body of literature regarding adult ICU patients and their families for prevalence of PTSD after critical illness in these three groups and identifies risk factors for the development of PTSD and suggestions for clinical implications and further research in this field.

Survivors of critical illness

The bulk of the literature investigating PTSD after critical illness has examined survivors of critical illness. Two systematic reviews of the topic recently have been published; the first looked at PTSD in 16 studies of medical ICU patients [2] and the second looked at survivors of all intensive care treatment [6]. For this review, only studies that evaluated the association between medical ICU admission and PTSD (or posttraumatic stress symptoms) are included, similar to the review by Jackson and colleagues [2]. In that review, studies were required to use quantitative or objective measures of PTSD. Studies of patients in surgical or trauma ICUs were excluded because of concern that the surgery or trauma itself may have elicited PTSD symptoms rather than the ICU experience. Five of these studies were prospective cohort studies [7–11] and one was a randomized controlled trial [12]. The remainder of the studies included six retrospective cohort studies [13–18] and four cross-sectional studies [19–22]. Since this review was

published, there have been two other prospective cohort studies published assessing prevalence of PTSD symptoms after critical illness [4,23]. Table 1 shows an overview of these studies.

The studies included in the review varied greatly in methodology. Criteria for entry into each study differed, including varied required lengths of stay in an ICU. Some studies investigated all medical intensive care patients, whereas others were restricted to those who had specific medical conditions, such as acute lung injury or septic shock. Patients in the studies varied regarding severity of illness and need for mechanical ventilation, both of which may affect the experience of ICU treatment. The numbers of subject included in each study ranged from 20 to 143. A few of the studies evaluated individuals at multiple time points [7,12,14,15,23]. In these, the initial evaluation occurred within 2 months of hospital discharge whereas follow-up evaluations occurred at varying time points, up to as many as 8 years after ICU discharge. The remaining studies surveyed patients at only one time point, which ranged from 3 months to 13 years after discharge from an ICU or hospital. Patient follow-up rates also varied in these studies, ranging from 24% to 84% [2].

Several, although not all, of the studies, excluded subjects who had prior psychiatric or neurologic illness [4,12,13,15,17,20]. The studies also varied in the method in which PTSD was measured and assessed. Nine of the studies used only standardized screening tools for assessment, including the Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10), Impact of Events Scale (IES), IES-Revised, Davidson Trauma Scale, Trauma Symptom Checklist-33, and Experience of Treatment in Intensive Care 7-Item Scale [4,7,8,11–13,16,18,20,21]. In most cases, these tools were administered in person; however, in two studies they were administered by telephone [18,20]. In this group of studies, the evaluation of PTSD was made solely on information gathered from these screening tools. Five of the studies used the Structured Clinical Interview for *DSM-IV* (SCID) after a screening tool suggested PTSD [9,14,15,17,19]. In general, these five studies showed lower prevalence of PTSD identified by the SCID. For example, one study showed that only 57% of the subjects who screened positive via the PTSS-10 were subsequently identified as having PTSD when followed-up with the SCID [19]. Most of these studies, however, did not assess using the SCID in patients who did not screen positive on a screening tool.

Prevalence of PTSD ranged from 5% in a prospective cohort study that used the IES [7] to 63% in the placebo group in a retrospective cohort study that used the PTSS-10 and SCID to measure PTSD (see Table 1) [13]. Several of the studies that reported higher prevalence of PTSD (54%, 59%, and 63%) had particularly small sample sizes or were subgroup analyses of larger populations [9,13,17]. There also was variation in the reported prevalence based on time of assessment of symptoms. Specifically, prevalence was highest when assessment occurred close to the time of discharge and decreased as time from discharge increased [2].

Table 1
Summary of studies assessing the prevalence of posttraumatic stress disorder in survivors of critical illness in the medical intensive care unit

Author and reference no.	Study design	Time between critical illness and assessment of posttraumatic stress disorder	Instrument used	Sample size	Response rate	Prevalence of posttraumatic stress disorder
Schelling, et al 1999 [17]	Retrospective cohort	2 to 9 years	PTSS-10, clinical interview	54	Unknown	38% (18.5% in treatment group, 59% in control group)
Schelling, et al 1998 [16]	Retrospective cohort	6 to 10 years	PTSS-10	80	78%	27.5%
Stoll, et al 1999 [15]	Retrospective cohort	2 time points at least 2 years apart (1 to 19 years after discharge)	PTSS-10, clinical interview	52	65%	25%
Eddleston, et al 2000 [10]	Prospective cohort	3 months	Selected PTSD questions	143	63%	36% with "distressing flashback"
Nelson, et al 2000 [22]	Cross-sectional	6 to 41 months (mean 19 months)	Seven items pertaining to PTSD	24	71%	39% with "bad memories or dreams"
Schelling, et al 2001 [13]	Retrospective cohort	21 to 49 months	PTSS-10, SCID	20	84%	40% (63% in placebo roup, 11% in treatment group)
Scragg, et al 2001 [20]	Cross-sectional	>5 years	IES, TSC-99, ETIC-7	60	56%	15% with PTSD (30% with posttraumatic s tress symptoms)
Shaw, et al 2001 [21]	Cross-sectional	Unknown	IES	20	N/A	35%
Jones, et al 2003 [12]	Randomized controlled trial	6 weeks and 6 months	IES	115 at 6 weeks, 102 at 6 months	80%	51% (at 6 months)

Kress, et al 2003 [9]	Prospective cohort	Approximately 1 year	IES-R, clinical interview	32	30%	18.5% (54% from control group, 0% from intervention group)
Cuthbertson, et al 2004 [8]	Prospective cohort	3 months	Davidson Trauma Scale	78	70%	14%
Kapfhammer, et al 2004 [14]	Retrospective cohort	Median of 8 years	PTSS-10, SCID	46	58%	23.9%
Nickel, et al 2004 [19]	Cross-sectional	Unknown	PTSS-10, SCID	41	N/A	9.76% with PTSD (17% with posttraumatic stress symptoms)
Capuzzo, et al 2005 [7]	Prospective cohort	1 week and 3 months	IES	63 at 3 months	73%	5%
Rattray, et al 2005 [11]	Prospective cohort	Hospital discharge, 6 months and 12 months	IES	67 at 6 months, 60 at 12 months	73%	20% with high avoidance scores, 18% with high intrusion scores
Deja, et al 2006 [18]	Retrospective cohort	57 +/− 32 months	PTSS-10	65	49.6%	29%
Girard, et al 2007 [4]	Prospective cohort	6 months	PTSS-10	43	24%	14%
Sukantarat, et al 2007 [23]	Prospective cohort	3 and 9 months	IES	51	88%	24%–38%

Several risk factors for PTSD were identified in these studies, although the methods used varied. Risk factors that were identified by more than one study include more delusional memories as opposed to factual memories [7,12,19], increased length of stay or duration of mechanical ventilation [8,11,14], greater levels of sedation or neuromuscular blockade [4,9,22], younger age [4,8,11,20], prior mental health history [8,19], and female gender [4,10,20]. In one study, greater perceived social support was implicated as protective against the development of PTSD [18].

In summary, it is difficult to provide a precise estimate of the prevalence of PTSD among survivors of critical illness, but these studies suggest it is significantly higher than seen in the general population and probably in the range of 14% to 50%. Several risk factors for the development of PTSD have been identified in those who are critically ill, including features of the ICU stay that correlate with higher severity of illness and length of stay and features of patients suggesting that some characteristics put individuals at increased risk.

Family members of survivors of critical illness

Far fewer studies have investigated the prevalence of PTSD in family members of individuals who survive their critical illness and these studies are outlined in Table 2 [5,24]. The largest of these was conducted in France by Azoulay and colleagues [5] and was a longitudinal study conducted in 21 medical-surgical ICUs in 2003. Family members were eligible for study if they came to an ICU to visit a patient who had an ICU stay of greater than 48 hours. The closest family member was identified and offered participation in the study. Telephone interviews were conducted 90 days after ICU discharge or death. Family members completed the IES, the 36-Item Short Form Health Survey (SF-36), and the Hospital Anxiety and Depression Scale. The investigators considered IES scores greater than 30 as the cutoff for posttraumatic stress reaction (PTSR), indicating a significant risk for PTSD. A total of 459 patients were screened for inclusion. Two hundred eighty-four family members consented and were able to be reached for follow-up. Of these, 228 were family members of ICU survivors whereas 56 were family members of individuals who died in an ICU.

In this study, 94 (33.1%) family members screened positive for PTSR with an IES score greater than 30 (see Table 2). When restricting analysis to those whose family members who survived their ICU stay, 28.9% of family members screened positive for PTSR. Factors independently associated with an IES score greater than 30 in family members included female gender, being a child of the ICU patient, history of cancer in the ICU patient, higher illness severity scores, feeling that information was incomplete, sharing in medical decision making in the ICU, and death of the patient in the ICU.

Table 2
Summary of studies assessing the prevalence of posttraumatic stress disorder in family members of survivors of critical illness

Author and reference no.	Study design	Time between critical illness and assessment of posttraumatic stress disorder	Instrument used	Sample size	Response rate	Prevalence of posttraumatic stress disorder
Azoulay, et al 2005 [5]	Prospective cohort	90 days	IES	284 total, 228 survivors	62%	33.1% in entire group; 28.9% in survivors
Jones, et al 2004 [24]	Randomized controlled trial	8 weeks, 6 months	IES	90 at 8 weeks, 84 at 6 months	86% at 8 weeks, 81% at 6 months	49% at 6 months

Other smaller studies have shown similar elevated prevalence of PTSD in family members of ICU survivors. A study by Jones and colleagues [24] was conducted as part of a randomized controlled trial of a rehabilitation program after discharge from an ICU. The investigators identified the closest family member of 104 recovering ICU patients. PTSD symptoms were assessed using the IES at 8 weeks and 6 months after ICU discharge. The investigators administered the interviews by telephone and used a cutoff of greater than 19 on the IES as indicative of symptoms of PTSD. There was no difference in IES scores between the control and intervention groups. IES scores in both groups were similar at the 8-week and 6-month interviews. The prevalence of an IES score greater than 19 was 49% at the 6-month interview.

One other smaller study looked at PTSD symptoms in family members during an ICU stay [25]. This study included 32 family members of ICU patients. The investigators used the IES to assess PTSD symptoms at two time points: (1) within 1 week of admission to an ICU and (2) just before anticipated ICU discharge. Using a cutoff IES score of 30, they found a prevalence of PTSD of 81% in family members at the first time point and 59% at ICU discharge. These individuals, however, did not meet *DSM-IV* criteria for PTSD as the measurements were made within 1 week of admission to an ICU and, therefore, symptoms attributable to the ICU could not have been present for the 1-month time period required for the diagnosis of PTSD by *DSM-IV* criteria.

In summary, family members of patients who survive critical illness are at increased risk for PTSD and estimates of the prevalence of PTSD in these family members suggest prevalence in the 25% to 50% range, although these studies are fewer in number. Risk factors are similar to those seen in patients and include female gender, prior psychiatric illness, and severity of illness of the patients. In addition, poor communication with health care providers seems to be associated with increased symptoms of PTSD.

Family members of those who die after critical illness

There are several studies that have looked at PTSD after bereavement not specific to ICUs. In one such study, widows and widowers were interviewed with the SCID 2 months after death of a spouse and the investigators found that 10% of widows and widowers met criteria for PTSD at that time [26]. They found no significant difference between types of death, when comparing deaths from chronic illness versus sudden, unexpected death. They did not discuss hospitalization or ICU admissions, however, before death in their study.

There are three published studies examining PTSD symptoms in families of patients who died (Table 3). The first study to specifically examine the prevalence of PTSD in family members of those who die in an ICU was that by Azoulay and colleagues [5] (discussed previously). In that study,

Table 3
Summary of studies assessing the prevalence of posttraumatic stress disorder in family members of patients who die after critical illness

Author and reference no.	Study design	Time between critical illness and assess-ment of posttraumatic stress disorder	Instrument used	Sample size	Response rate	Prevalence of posttraumatic stress disorder
Azoulay, et al 2005 [5]	Prospective cohort	90 days	IES	56 families of those who died	62%	50%
Laurtrette, et al 2007 [27]	Randomized controlled trial	90 days	IES	126	86%	45% in intervention group, 67% in control group
Gries, et al 2008 [28]	Retrospective cohort	6 to 36 months	PTSD Checklist-Civilian Version	196	71%	15.3%

56 family members of patients who died were interviewed with the IES at 90 days after death. Again, the overall prevalence of PTSD, defined by IES greater than 30, in the total study population (families of those who survived and those who died) was 33.1%. When looking at the subgroup of family members of those who had died, the prevalence of PTSD was 50%. Median IES scores were higher, as was prevalence of those who had IES scores greater than 30, in family members of patients who died in an ICU after decisions to limit life-sustaining treatments (60%), and in family members who were involved in decisions to limit life-sustaining treatments (80%).

Based on their results, the French group followed up that study with an intervention with the goal of reducing the burden of psychologic symptoms in family members whose loved ones died in an ICU [27]. This study enrolled family members of 126 patients who died in an ICU in France. Participants were randomly assigned to the intervention, which included a structured end-of-life care family conference and a bereavement brochure for the family, or to usual care. Interviews were conducted using the IES to assess PTSD 90 days after death. They found lower prevalence of PTSD, using IES scores of greater than 30, in the intervention group (45% versus 67%). The primary differences between the intervention and control group experiences were attributed to clinician-family communication. In addition, family members in the intervention group spent more time in family conferences and more of the conference time talking than did the control group.

More recently a study from the United States examined the level of symptoms of PTSD in family members of 196 patients who died in an ICU using the PTSD Checklist-Civilian Version between 6 and 36 months after death [28]. This study found a prevalence of 15.3% and found that the prevalence decreased with increasing time between death and survey administration. Other factors associated with increased symptoms of PTSD included female gender, history of medication use for emotions by the family member before the critical illness, and a history of the family member seeing a psychiatrist, neurologist, or pain specialist before the critical illness.

In summary, family members of patients who die in an ICU also seem at increased risk for PTSD in the general population and prevalence estimates include a broad range, from 15% to 65%. Risk factors include female gender and prior use of medications for emotions or seeing a psychiatrist before the critical illness [28].

Limitations of current research

There are several challenges to studying PTSD in general and particularly in this population after critical illness. The diagnosis of PTSD requires not only symptoms of distress but also a precipitating traumatic event. There is significant comorbidity with PTSD and other psychiatric illnesses [1]. As such, it often is difficult to decipher the cause of PTSD symptoms and the relative contribution of PTSD to an individual's overall level of distress.

In studies in ICUs in particular, the assessment of PTSD that is related to ICU care is challenging. It is difficult to separate the experience of an ICU from other aspects of health care and illness. It also is challenging in this research setting to ensure that the traumatic event of interest is, in fact, the ICU experience, and that other traumatic events that may have been experienced in the past are not contributing to symptoms at the time of assessment.

The studies that have looked at PTSD in the setting of critical care have significant methodologic limitations. Most of these studies likely overestimate the prevalence of PTSD by using only screening tools for diagnostic purposes. These screening instruments are not designed to definitively identify the presence, absence, or severity of PTSD. Although some of the studies (discussed previously) did follow-up with the SCID, most did not. In the case of PTSD in family members, all relied on screening tools alone (although one recent study used the SCID to assess anxiety, depression, and complicated grief in family members of patients who died in an ICU) [29]. Most screening tools, including that used most commonly, IES, have not been validated in patients who have had critical illness.

Additionally, most of the published studies on this topic have limited sample sizes. Among studies of ICU survivors, the largest study had 150 patients in follow-up whereas most had fewer than 50 patients. There are problems with low follow-up rates and the potential for nonresponse bias in the samples. Although it is difficult to assess the direction of the bias introduced by nonresponse or loss to follow-up, the avoidant symptoms of PTSD suggest that these studies with significant nonresponse rates may underestimate the burden of PTSD.

Finally, there are difficulties generalizing published results to all ICU patients and their families. In the case of the French study of PTSD in family members, it is difficult to generalize these results to the United States population. Prior studies in the United States have shown that family members of critically ill patients are more satisfied with care when they are involved in the decision-making process at the end of life [30], which seems contrary to the finding by Azoulay and colleagues [5] where there was increased prevalence of PTSD in family members involved in end-of-life decision making.

Relevance to critical care clinicians

It is important that critical care clinicians be aware that PTSD is a potential morbidity of critical illness for patients who survive their illness and for family members of those who survive or die after their critical illness. Although the diagnosis of PTSD can be made only after the incident of critical illness and, therefore, is beyond the scope of practice for most critical care clinicians, it may be important to be aware of potential risk factors for this morbidity during the course of critical illness and to counsel patients

and families that psychologic distress may occur after an ICU course. In this way, patients and family members may be more aware of the risk for development of these symptoms and may be able to seek appropriate counseling and therapy as needed once the critical illness has ended.

Summary

Despite the limitations (described previously), there is consistent evidence in the literature that the prevalence of PTSD in survivors of critical care is elevated above that seen in the general population. Similarly, prevalence for family members of survivors and those who died during their ICU stay are elevated. The experience of an ICU, for patients and their families, has the potential to cause significant psychologic distress. PTSD is an important sequela of critical illness and should be considered by health care providers when providing post-ICU care to survivors and their families and to families of those who die in an ICU. Increased recognition, and perhaps screening, may be important as there are effective treatments available [1].

Future studies are needed to further assess the prevalence and burden of PTSD in these three groups. It would be beneficial not only to screen for PTSD symptoms but also to follow-up positive screening with structured clinical interviews. With increased awareness of PTSD as a common sequela of critical illness, future interventions should be investigated to prevent and to treat this adverse outcome in patients and family members. The French study by Laurtrette and colleagues [28] is promising, showing decreased symptom burden with communication-based intervention for families. Additional interventions should be considered for patients and for family members of ICU patients who are not expected to die.

References

[1] Yehuda R. Post-traumatic stress disorder. N Engl J Med 2002;346(2):108–14.
[2] Jackson JC, Hart RP, Gordon SM, et al. Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. Crit Care 2007;11(1):R27.
[3] Diagnostic and statistical manual of mental disorders, 4th edition: DSM-IV. Washington, DC: American Psychiatric Association; 1994.
[4] Girard TD, Shintani AK, Jackson JC, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care 2007;11(1):R28.
[5] Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med 2005;171:987–94.
[6] Griffiths J, Fortune G, Barber V, et al. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Med 2007;33:1506–18.
[7] Capuzzo M, Valpondi V, Cingolani E, et al. Post-traumatic stress disorder-related symptoms after intensive care. Minerva Anestesiol 2005;71(4):167–79.
[8] Cuthbertson BH, Hull A, Strachan M, et al. Post-traumatic stress disorder after critical illness requiring general intensive care. Intensive Care Med 2004;30(3):450–5.

[9] Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med 2003;168(12): 1457–61.
[10] Eddleston JM, White P, Guthrie E. Survival, morbidity, and quality of life after discharge from intensive care. Crit Care Med 2000;28:2293–9.
[11] Rattray JE, Johnston M, Wildsmit JA. Predictors of emotional outcomes of intensive care. Anaesthesia 2005;60(11):1085–92.
[12] Jones C, Skirrow P, Griffiths RD, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med 2003;31:2456–61.
[13] Schelling G, Briegel J, Roozendaal B, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry 2001;50: 978–85.
[14] Kapfhammer HP, Rothenhausler HB, Krauseneck T, et al. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. Am J Psychiatry 2004;161:45–52.
[15] Stoll C, Kapfhammer HP, Rothernhausler HB, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. Intensive Care Med 1999;25(7):697–704.
[16] Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 1998;26(4): 651–9.
[17] Schelling G, Stoll C, Kapfhammer HP, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. Crit Care Med 1999;27(12):2678–83.
[18] Deja M, Denke C, Weber-Carstens S, et al. Social support during intensive care unit stay might improve mental impairment and consequently health-related quality of life in survivors of severe acute respiratory distress syndrome. Crit Care 2006;10(5):R147.
[19] Nickel M, Leiberich P, Nickel C, et al. The occurrence of posttraumatic stress disorder in patients following intensive care treatment: a cross-sectional study in a random sample. J Intensive Care Med 2004;19(5):285–90.
[20] Scragg P, Jones A, Fauvel N. Psychological problems following ICU treatment. Anaesthesia 2001;56(1):9–14.
[21] Shaw RJ, Harvey JE, Nelson KL, et al. Linguistic analysis to assess medically related posttraumatic stress symptoms. Psychosomatics 2001;42:35–40.
[22] Nelson BJ, Winert CR, Bury CL, et al. Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med 2000;28:3626–30.
[23] Sukantarat K, Greer S, Brett S, et al. Physical and psychological sequelae of critical illness. Br J Health Psychol 2007;12(1):65–74.
[24] Jones C, Skirrow P, Griffiths RD, et al. Post-traumatic stress disorder-related symptoms in relatives of patients following intensive care. Intensive Care Med 2004;30:456–60.
[25] Paparrigopoulos T, Melissaki A, Efthymiou A, et al. Shortterm psychologic impact on family members of intensive care unit patients. J Psychosom Res 2006;61:719–22.
[26] Zisook S, Chentsova-Dutton Y, Shuchter SR. PTSD following bereavement. Ann Clin Psychiatry 1998;10(4):157–63.
[27] Laurtrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med 2007;356:469–78.
[28] Gries C, Engelberg R, Kross E, et al. Risk of PTSD and depression in family members after the death of a critically ill patient. Am J Respir Crit Care Med 2008;177:A515.
[29] Siegel MD, Hayes E, Vanderwerker LC, et al. Psychiatric illness in the next of kin of patients who die in the intensive care unit. Crit Care Med 2007;36(6):1722–8.
[30] Gries CJ, Curtis JR, Wall RJ, et al. Family member satisfaction with end-of-life decision making in the ICU. Chest 2008;133(3):704–12.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 889–919

CRITICAL
CARE
CLINICS

Neuropsychiatric Aspects of Infectious Diseases

Stephen J. Ferrando, MD[a,*],
Zachary Freyberg, MD, PhD[b]

[a]*The New York-Presbyterian Hospital, Weill Medical College of Cornell University, 525 East 68th Street, Box 181, New York, NY 10065, USA*
[b]*Center for Molecular Recognition, Columbia University, 630 West 168th Street, Box 7, New York, NY 10032, USA*

Among the critically ill, infectious diseases can play a significant role in the etiology of neuropsychiatric disturbances. All critical care physicians are familiar with delirium as a secondary complication of systemic infection. This article focuses on key infectious diseases that commonly and directly produce neuropsychiatric symptoms, including direct infection of the central nervous system (CNS).

HIV infection and AIDS

HIV-AIDS is often seen as the modern "great imitator," a complex infectious disease with multiple manifestations and interplay of myriad biopsychosocial factors, including neuropsychiatric disorders related to direct HIV-1 brain invasion, CNS opportunistic infections, manifestations of concurrent drug abuse, hepatitis C coinfection, and iatrogenic complications. Differential diagnosis and management of HIV-AIDS–related neuropsychiatric disturbances can serve as a paradigm for other infectious diseases that have neuropsychiatric manifestations.

Medical hospitalization in HIV-AIDS

With the widespread availability of highly active antiretroviral therapy (HAART) for HIV infection in developed countries, there have been dramatic declines in HIV-related hospital admissions. Between 1995 and 1997, admissions dropped 33% to 75% [1–4]. Since that time, rates have

* Corresponding author.
E-mail address: sjferran@med.cornell.edu (S.J. Ferrando).

0749-0704/08/$ - see front matter
doi:10.1016/j.ccc.2008.05.007 *criticalcare.theclinics.com*

stabilized or rebounded slightly. The reasons for medical hospital admission have also shifted. In two urban hospital studies [3,4], a drop in hospitalization caused by opportunistic infections and cancers was observed, contrasting with a rise in nonopportunistic complications, such as hepatitis C and cardiovascular disease. Mean CD4 counts of HIV inpatients were seen to increase by over 100 cells/mm^3 from 1995 to 2001 [3].

Factors that seem to confer risk for medical hospitalization in the HAART era include low CD4 count, female gender, lack of antiretroviral treatment, and injection drug use [3,4]. The sociodemographic characteristics of those at risk reflect the shifting demographics of the HIV epidemic, limitations in access to care, and poor adherence to antiretroviral treatment.

Epidemiology of psychiatric disorders in HIV-AIDS medical inpatients

There are extensive epidemiologic data regarding psychiatric disorders in ambulatory HIV-AIDS patients. Overall, studies reveal high rates of lifetime and current substance abuse and depressive and anxiety disorders (see Ferrando and Tiamson [5] for a review of this literature). As seen in Table 1, among medially hospitalized HIV patients, studies indicate a similar profile; however, delirium, dementia, and manic-spectrum disorders seem to be more common [6–10]. The most frequently diagnosed disorders are in the depressive spectrum (range, 27%–83%), including depression secondary to medical condition (or organic mood disorder), adjustment disorder with depressed mood, major depressive disorder, or dysthymic disorder. Delirium is diagnosed in 8% to 29% of patients, regardless of HIV stage, and is often reported to be concurrent with HIV-associated dementia, diagnosed in 8% to 22% of cases. Substance use disorders are diagnosed in 11% to 36% of AIDS inpatients and up to 63% in HIV-positive, non-AIDS patients. One study found that bipolar disorder and HIV-associated mania occurred in 11% of medical inpatients [10].

HIV and the brain

Since the beginning of the HIV epidemic, it has been recognized that HIV can infect the CNS and produce a range of cognitive and behavioral symptoms that become more frequent and severe as the immune system declines and symptomatic illness and AIDS ensue. In 1991, the American Academy of Neurology published research diagnostic criteria for HIV-associated cognitive, motor, and behavior disorders [11], which remained in widespread use until the diagnostic criteria were recently updated by a work group convened at the National Institutes of Mental Health [12]. Based on cumulative research and clinical evidence, this group described three HIV-associated neurocognitive disorders: (1) asymptomatic neurocognitive impairment, (2) mild neurocognitive disorder, and (3) HIV-associated dementia. The asymptomatic neurocognitive impairment category recognizes that a substantial percentage of HIV-infected patients have demonstrable impairment

Table 1
Frequency of psychiatric disorders reported in the inpatient medical setting

	N	% Male	HIV risk	Medical illnesses	Depressive disorders	% Dementia	% Delirium	% Substance use disorder	% Other psychiatric disorders
Perry SW and Tross S, 1984	52 AIDS	98	Homosexual 79% Homosexual + IVDU 12% Other 9%	OI 71% KS 17% OI+KS 12%	Any 83%	11	29	11	Schizophrenia 2
Dilley JW et al, 1985	13 AIDS	100	Homosexual 100%	OI 70% OI+KS 15% Other 15%	Adjustment disorder 54% MDD 15%	8	8	31	Panic 8
O'Dowd MA and Mc Kegney P, 1990	67 AIDS	69	Not reported	Not reported	Adjustment disorder 42% MDD 3%	22	27	20	Axis II 6
Bialer P et al, 1996	433 AIDS 116 HIV+	79	Not Reported	Not Reported	Organic mood 13% Adjustment disorder 13% MDD 1%	22	29	36	Axis II 9
Ferrando SJ et al, 1997	36 AIDS 4 HIV+	60	Homosexual 34% IVDU 31% Heterosexual 31%	OI 89%	MDD or 31% dysthymic disorder	19	19	19	Mania/ hypomania 11 Anxiety 8

Abbreviations: IVDU, intravenous drug user; KS, Kaposi's sarcoma; MDD, major depressive disorder; OI, opportunistic illnesses.

on neuropsychologic testing but little or no perceptible functional impairment. The latter two disorders (mild neurocognitive disorder and HIV-associated dementia) present with cognitive and behavioral symptoms associated with functional impairment (mild in mild neurocognitive disorder, moderate to severe in HIV-associated dementia). HIV-associated neurocognitive disorders have been found to predict shorter survival [13,14], especially in the setting of virologic failure on HAART [15]. The cognitive symptoms of HIV-associated neurocognitive disorders are characteristic of subcortical-frontal pathology and include impairment in psychomotor processing speed, executive function, and verbal memory. The potential behavioral manifestations are broad and include apathy, depression, anxiety, mania, and psychosis.

Neuropathologically, HIV traverses the blood-brain barrier primarily by infected blood mononuclear cells, becoming activated macrophages once they enter the brain. Neuropathologic changes seem to be a result of CNS immune activation with release of neurotoxic cytokines and metabolites. Substance abuse is an important cofactor for HIV neuropathology [16]. Subcortical brain structures, such as the basal ganglia and periventricular white matter, are most affected. If unchecked, this immune cascade leads to neuronal cell apoptosis. Effective suppression of CNS viral replication and the resulting immune activation has the potential, however, to reverse at least some of the neuropathologic changes.

HIV-associated neuropathology has received heightened attention in recent years because of two associated developments. First, HIV-1 viral load monitoring has demonstrated that the CNS is an independent sanctuary site of viral replication [17]. The level and genetic profile of HIV in the peripheral circulation may not correlate with that in the CNS. The second development relates to the recognition that antiretroviral medications have differing levels of penetration into the CNS. It is hypothesized that poorly penetrating antiretrovirals might inadequately treat CNS infection despite being effective peripherally. This has led to concerns that actively replicating virus in the CNS could cause progressive cognitive decline in otherwise healthy HIV-positive individuals and could also lead to a reseeding of the virus into the peripheral circulation. Indeed, better CNS antiretroviral penetrance has been found to correlate with better suppression of HIV in the cerebrospinal fluid (CSF) [18]. The past 10 years have seen a reduction in the incidence of HIV-associated dementia from 7% per year in the pre-HAART era to approximately 2% to 3% [19]. HAART regimens have been shown to reduce CSF viral load to undetectable levels [17], to reverse white matter lesions on MRI [20], to reverse brain metabolic abnormalities detected by proton MR spectroscopy [21], and also to improve neuropsychologic test performance [22,23]. Despite these hopeful findings, however, functionally significant cognitive and behavioral disturbances, without frank dementia, may persist in approximately one fourth of HAART-treated patients [24,25], impeding adherence to treatment [26] and ability to work [27].

Differential diagnosis

Differential diagnosis is paramount when investigating for medical and neuropsychiatric etiologic factors related to HIV illness and its treatment (Box 1).

First, in assessing the hospitalized HIV-AIDS patient, it is important to query for personal and family psychiatric history because neuropsychiatric complications may be a manifestation of pre-existing psychopathology [28,29]. Even in the presence of a prior psychiatric history, however, it is imperative to rule out potentially exacerbating, if not etiologic, medical factors. HIV-associated neurocognitive disorders are associated with a range of cognitive or behavioral symptoms, including apathy, depression, sleep disturbances, mania, and psychosis. CNS opportunistic illnesses and cancers can also present with a wide range of neuropsychiatric symptoms as a result of both focal and generalized neuropathologic processes (see Table 2).

Substance intoxication and withdrawal are also common in the medical inpatient setting. HIV-infected substance users have high rates of pre-existing comorbid psychopathology that may be exacerbated by ongoing substance use. Further, abuse of multiple substances concurrently (eg, opioids, cocaine, benzodiazepines, alcohol) can result in complex intoxication and withdrawal states that may be very difficult to treat.

Hepatitis C coinfection is associated with multiple neuropsychiatric complaints, most frequently fatigue, depression, and cognitive dysfunction. The pattern of cognitive impairment is similar to that of HIV, with impairment in attention, concentration, psychomotor processing speed, verbal memory, and executive dysfunction. Patients with end-stage liver disease and cirrhosis experience superimposed delirium (hepatic encephalopathy). Combination pegylated interferon alpha-2a treatment for hepatitis C has been extensively documented to cause neuropsychiatric side effects including depression,

Box 1. Differential diagnosis of psychiatric disorders and symptoms in HIV-AIDS medical inpatients

- Primary psychiatric disorder
- CNS HIV infection (minor neurocognitive disorder and HIV-associated dementia)
- CNS opportunistic illnesses and cancers (Table 2)
- Substance intoxication and withdrawal
- Neuropsychiatric complications of hepatitis C and its treatments
- Neuropsychiatric side effects of HIV medications
- Drug-drug interactions
- Endocrine abnormalities (eg, hypogonadism, adrenal insufficiency, thyroid disease)

Table 2
Opportunistic illnesses of the central nervous system in AIDS

OI	CD4	Signs	Focal	CT/MRI	Lumbar puncture
Toxoplasmosis	<100	Fever Delirium Headache Seizures	Y	Ring-enhancing lesions Basal ganglia Gray-white junction	*T gondii* antibody or PCRHigh specificity/ low sensitivity Other routine CSF studies not generally diagnostic
Cytomegalovirus	<50	Delirium Infections found at diagnosis Retina Blood Adrenal gland Gastrointestinal tract	Y/N	Ventricular enlargement Increased periventricular signal (T2 image)	CMV PCR Variable specificity/ variable sensitivity Elevated protein level, pleocytosis, hypoglycorrhachia
Cryptococcal meningitis	<100	Fever Delirium Not universally seen Increased intracranial pressure (50%) Seizures	N	Nonspecific	C*neoformans*, India ink, latex agglutination or PCR High specificity/high sensitivity Other routine CSF studies not generally diagnostic

Progressive multifocal leukoencephalopathy (JCV)	<100	Mono/hemiparesis Dysarthria Gait disturbance Sensory deficit Progressive dementia Occasional Visual loss Seizures	Y	Attenuated signal/ (T2 images) Periventricular White matter Other areas: Gray matter Brainstem Cerebellum Spinal cord	JCV PCR High specificity/high sensitivity Other routine CSF studies not generally diagnostic
Central nervous system neoplasm/ lymphoma	<100	Afebrile Delirium Seizures (10%) Increased intracranial pressure	Y	Lesions Hypodense/ patchy Nodular Enhancing SPECT thallium differentiates from toxoplasmosis	EBV PCR High specificity/high sensitivity Other routine CSF studies not generally diagnostic

Abbreviations: CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; JCV, JC virus; OI, opportunistic illnesses; PCR, polymerasquf;e chain reaction; SPECT, single-photon emission CT.

suicidal ideation, anxiety, sleep disturbance, fatigue, mania, psychosis, delirium, and cognitive dysfunction [30].

Multiple antiretroviral and other medications used in the context of HIV have been reported to have neuropsychiatric side effects. These include zidovudine [31], didanosine [32], abacavir [33], nevirapine [34], efavirenz, and interferon alpha-2a. Most of these are uncommon or rare and causal relationships are often difficult to determine. The most widespread clinical concern has been generated by reports of sudden-onset depression and suicidal ideation associated with interferon alpha-2a and efavirenz. Early reports suggested that efavirenz may be associated with at least transient neuropsychiatric side effects in excess of 50% of patients [35]. Reported effects are protean and include depression, suicidal ideation, vivid nightmares, anxiety, insomnia, psychosis, cognitive dysfunction, and antisocial behavior.

Drug interactions between antiretroviral and psychotropic medications are important aspects of differential diagnosis in the hospital setting. In one study, HIV-AIDS medical inpatients were prescribed an average of seven medications during their admission [10]. Factors influencing drug-drug interactions include medical illness severity, prior substance abuse, the likelihood of multiple medications being initiated simultaneously, changes in volume of distribution and protein binding, and hepatic and renal impairment.

HIV-AIDS inpatients often experience endocrinologic derangements that may produce behavioral symptoms. These include clinical and subclinical hypothyroidism [36], hypogonadism [37], and adrenal insufficiency [38], and Graves' disease (autoimmune thyroiditis) [36]. Thyroid deficiency, including its subclinical forms, is present in approximately 16% of HIV-infected patients [36]. Testosterone deficiency, with clinical symptoms of hypogonadism, is present in up to 50% of men with symptomatic HIV or AIDS and is likely to be present with concurrent acute medical illness [37]. Deficiency of adrenal glucocorticoid production is present in up to 50% of severely ill HIV patients [38]. These endocrine deficiency states have been associated with fatigue, low mood, low libido, and loss of lean body mass and may be ameliorated by correction of the deficiency. Graves' disease presents in the acute stages with activation symptoms including anxiety, irritability, insomnia, weight loss, mania, and agitation.

Diagnostic evaluation

The psychiatric evaluation of the HIV-AIDS inpatient is consistent with the broad differential diagnosis and is focused on identifying potentially reversible underlying etiologies. A thorough psychiatric evaluation, including presenting symptoms, personal and family history of psychiatric illness and substance abuse, and a cognitive functioning examination are essential. Box 2 contains a listing of such diagnostic tests.

In general, the diagnostic work-up should include complete blood count with differential; serum chemistries (including liver and renal function tests,

Box 2. Diagnostic evaluation of the medical inpatient with HIV-AIDS and neuropsychiatric disturbances

- Medical evaluation with screening laboratories: complete blood count, chemistry screen (including liver and renal function tests), urinalysis, chest radiograph, electrocardiogram, blood and urine cultures (when applicable)
- Psychiatric diagnostic interview including personal and family history
- Cognitive screen (HIV Dementia Scale)
- Additional laboratories when applicable: illicit drug toxicology screen, serum psychotropic drug levels, thyroid function tests, antithyroid antibodies, vitamin B_{12} and B_6 levels, total or bioavailable testosterone, dehydroepiandrosterone sulfate, adrenocorticotropic stimulation test, 24-hour urine cortisol
- Evaluation for hepatitis C (including viral load)
- Review of antiretroviral regimen for neuropsychiatric side effects
- Review of psychotropic mediations for efficacy, neuropsychiatric side effects, drug interactions
- Neuroimaging (MRI, MR spectroscopy)
- Lumbar puncture

fasting glucose, and creatine phosphokinase); chest radiograph; electrocardiogram; blood and urine cultures (if indicated); toxicology screen; and psychotropic medication serum levels (when available). Depending on the clinical presentation, assays of thyroid function, vitamins B_6 and B_{12}, Venereal Disease Research Laboratory, serum total, free or bioavailable testosterone, adrenocorticotropic hormone stimulation, and 24-hour urinary cortisol may be obtained. If brain imaging is required, MRI of the brain with gadolinium contrast is preferred over CT because it produces better visualization of brain tissue and of subcortical and posterior fossa structures and focal lesions. A lumbar puncture may also be obtained if necessary under sedation with fluoroscopic guidance. Results are often nonspecific, but important studies include opening pressure; culture (viral, fungal, mycobacterial); cell count; protein; neopterin; β_2-microglobulin; and polymerase chain reaction testing for cytomegalovirus, Epstein-Barr virus, JC virus, herpes simplex virus (HSV), and HIV-1.

Psychiatric disorders in HIV-AIDS and their treatment

Depression

Depression is the most common psychiatric symptom and diagnosis among medical inpatients with HIV-AIDS. Symptoms are often attributed

to adjustment disorder or to medically related (organic) factors that may be transient, related to improvement in physical symptoms. In one prospective study assessing depressive symptoms at admission and discharge, however, 28% of HIV-AIDS medical inpatients had severe depression that persisted at discharge [39]. In another study, 76% of patients who had a depressive disorder during their admission continued to have significant depressive symptoms 3 to 6 weeks after discharge, with significant predictors of depression during and after medical hospitalization being female gender, AIDS diagnosis, and poor social support [10].

In the medical inpatient setting in particular, the diagnosis of depressive disorder in HIV-infected patients may be confounded by somatic symptoms common to depression, HIV illness, and its complications. These include fatigue, appetite loss, sleep disturbance, and cognitive disturbances. Generally, in the presence of persistent depressed mood or loss of interest, an inclusive approach toward somatic symptoms is preferred. This is based on the fact that affective and somatic subscales of depression screening instruments (eg, the Beck Depression Inventory) are highly intercorrelated, that these symptoms are more closely linked to measures of depression than to measures of HIV-disease severity, and that both affective and somatic symptoms improve with antidepressant treatment [40,41].

In the medical inpatient setting, when antidepressant medication treatment is considered, particular attention must be paid to side effect profile, hepatic and renal function, and the potential for drug interactions. In addition to standard antidepressants, such as serotonin and serotonin-norepinephrine reuptake inhibitors, the initiation of psychostimulants and anabolic steroids, particularly testosterone, is frequently used in the inpatient setting and is given particular attention here.

Psychostimulants have been studied for the treatment of depressed mood, fatigue, and cognitive impairment in the context of HIV infection, particularly in advanced illness and where rapid onset of action is desirable. Agents studied include methylphenidate (5–90 mg/day); dextroamphetamine (5–20 mg/day); pemoline (35–150 mg/day); and the wakefulness agent modafinil (50–200 mg/day) [42–45]. These agents are efficacious in treating depressive symptoms in patients with advanced HIV. The primary side effect is overstimulation.

Testosterone deficiency, with clinical symptoms of hypogonadism (depressed mood, fatigue, diminished libido, decreased appetite, and loss of lean body mass) is present in up to 50% of men and women with symptomatic HIV or AIDS [37]. The most common screening test for testosterone deficiency is total serum testosterone (deficiency is defined as less than 300–400 ng/dL in men); however, serum-free (deficiency: $<$5–7 pg/mL in men; $<$3 pg/mL in women) and bioavailable testosterone may be more accurate measures. For testosterone replacement in men, commonly used testosterone preparations include esterified depot testosterone (propionate, enanthate, cypionate, initiated at 100–200 mg intramuscularly every 2 weeks,

maximum 400 mg intramuscularly weekly), transdermal skin patches (one to two patches, 5–10 mg, to clean dry skin daily), and transdermal testosterone gel (one to four packets, 25–100 mg, to clean dry skin daily), with the depot preparations being the least expensive and most studied. Patch and gel formulations may produce less variability in serum testosterone levels and in target symptoms. In women, transdermal testosterone, 150 μg per day or equivalent, may be used to improve energy, well-being, muscle mass, and restore normal menstrual functioning [37]. Reported side effects for men include irritability, tension, reduced energy, hair loss, testicular atrophy, reduced ejaculate volume, and acne. For women, there is particular concern for virilizing side effects; however, clinically these have been minimal in the setting of physiologic replacement dosing in the range described.

Delirium

Delirium is diagnosed in 11% to 29% of hospitalized HIV-AIDS patients [10]. There are no data regarding specific or distinguishing symptom characteristics for the delirium seen in HIV patients. Both the hypoactive and hyperactive variants of delirium are seen, and in addition to cognitive disturbance, symptom manifestations include apathy, dysphoria, agitation, fearfulness, delusions, and hallucinations [46].

Delirium in the HIV-AIDS patient is often superimposed on HIV-associated neurocognitive disorders, particularly dementia, and patients with these disorders are at increased risk for the development of delirium when medically hospitalized. The etiology of delirium in HIV-AIDS patients is generally multifactorial. Breitbart and colleagues [46] reported a mean of 12.6 medical complications in 30 delirious AIDS patients, with the most common being hematologic (anemia, leukopenia, thrombocytopenia, hypoalbuminemia) and infectious diseases (eg, septicemia, systemic fungal infections, *Pneumocystis carinii* pneumonia, tuberculosis, and disseminated viral infections). Other potential etiologies are discussed previously in the differential diagnosis section.

Central to the treatment of delirium is treatment of its underlying medical causes. Symptomatic treatment includes educational, environmental, and psychopharmacologic interventions. Education regarding the risk and nature of delirium delivered to patients, their family, and the treatment team can be preventative and can result in earlier treatment and improved outcomes. Environmental interventions include titrating the level of stimulation, sitting the patient up, placing patients next to a window, frequent orientation, stabilizing sleep-wake cycles, and placing familiar people and orienting objects in the room.

In terms of pharmacologic treatment, most practitioners treat delirium with atypical antipsychotics, including olanzapine (available with dissolving oral preparation and intramuscularly); risperidone (available in dissolving oral preparation); quetiapine; aripiprazole (available intramuscularly); and ziprasidone (available intramuscularly). The only double-blind clinical trial

of delirium treatment in AIDS, however, compared haloperidol, chlorpromazine, and lorazepam [46]. In that study, Breitbart and colleagues [46] screened HIV medical inpatients for delirium. Treatment was initiated early, and when symptoms were mild to moderate in degree. Patients were severely medically ill, because 9 (30%) of the 30 patients died within 1 week after completing the protocol. There were three important findings. First, haloperidol (mean dose, 2.8 mg/day acutely and 1.4 mg/day maintenance) and chlorpromazine (mean dose, 50 mg/day acutely and 36 mg/day maintenance) were equally efficacious. Second, the lorazepam arm (mean dose, 3 mg acutely) was stopped early because of worsening of delirium symptoms, including oversedation, disinhibition, ataxia, and increased confusion. Third, adverse effects in the antipsychotic arms were limited and included mild extrapyramidal symptoms (EPS), such as decreased expressiveness, rigidity, tremor, and mild akathisia.

Delirium is common in hospitalized HIV-AIDS patients, who should be assessed frequently for early detection and treatment. A combination of psychoeducational, environmental, and pharmacologic interventions, primarily with neuroleptic medications, is recommended. Benzodiazepines should be avoided, except in cases of severe agitation that fails to respond to antipsychotic agents or patients experiencing delirium secondary to alcohol or other CNS-depressant agent withdrawal, and patients should be monitored closely for the emergence of EPS.

Mania

Manic symptomatology has been reported in 11% of all medically hospitalized HIV-AIDS patients [10] and may be seen in conjunction with primary bipolar illness or with CNS HIV infection (HIV-associated mania). Descriptively, HIV-associated mania is found to be a late-onset, secondary affective illness associated with HIV infection of the brain, being less associated with a personal or family history of mood disorder. In addition, the symptomatology of HIV-associated mania may include more irritability, less hypertalkativeness, and more psychomotor slowing and cognitive impairment compared with primary bipolar mania. Given that HIV-associated mania is directly related to HIV brain infection, antiretroviral agents that penetrate the blood-brain barrier may offer some protection from incident mania [47].

Practice guidelines recommend lithium, valproic acid, or oxcarbazepine and carbamazepine as standard therapy for a manic episode of bipolar affective illness. In the context of HIV infection, however, there are particular considerations regarding their use. These include concern over the low therapeutic index of lithium, the potential for valproic acid to stimulate HIV-1 replication in cell culture models, and the enzyme-inducing and hematologic side effects of oxcarbazepine and carbamazepine.

There is relatively little research on the psychopharmacologic treatment of HIV-associated mania. A case report on the use of lithium for

HIV-associated mania in an AIDS patient showed control of symptoms at a dosage of 1200 mg daily; however, significant neurotoxicity (cognitive slowing, fine tremor) occurred, leading to discontinuation [48]. The most commonly used mood stabilizer in the treatment of HIV-associated mania is valproic acid. Valproic acid, up to 1750 mg daily, led to significant improvement in acute manic symptoms, at serum levels more than 50 μg/L, with few adverse effects [49]. There have been reports of valproic acid increasing HIV replication in vitro in a dose-dependent manner, and one report of increased cytomegalovirus replication, perhaps mediated by alterations in intracellular glutathione, which is an important mediator of HIV replication. The clinical relevance of these findings remains controversial, and there are no reports of valproic acid causing elevations in viral load in vivo. Most recently, the anticonvulsant lamotrigine has received Food and Drug Administration approval for maintenance therapy in bipolar illness. It has been tested for HIV-associated peripheral neuropathy and may be useful for treating mixed mania or bipolar depression in HIV; however, patients with overt manic symptomatology generally require a traditional mood stabilizer. This anticonvulsant requires careful upward dose titration because of risk of severe hypersensitivity (Stevens-Johnson syndrome).

Given the limitations of mood stabilizers in HIV, there is widespread clinical use of atypical antipsychotics for acute and maintenance treatment of HIV-associated mania; however, there are no clinical trial data. Clinicians generally choose olanzapine, risperidone, or quetiapine as alternatives to traditional mood stabilizers; however, these agents may exacerbate metabolic syndrome or cause extrapyramidal symptoms in patients with extensive basal ganglia HIV involvement. Benzodiazepines may be useful for adjunctive treatment, but acute and maintenance therapy may be complicated by tolerance, dependence, and cognitive impairment, including the possibility of causing delirium and disinhibition.

Psychosis

HIV infection may be directly linked to the onset of psychosis, which is defined by the presence of thought disorder, hallucinations, or delusions. Psychosis in HIV is most often a manifestation of substance intoxication or withdrawal, delirium, HIV-associated neurocognitive disorders, mood disorders with psychotic features, or schizophrenia. Estimates of the prevalence of new-onset psychosis in patients with HIV range from 0.5% to 15% [50]. One study compared 20 HIV-infected patients with new-onset psychosis (and no prior psychotic episodes or current substance abuse) with 20 demographic and HIV illness-matched nonpsychotic patients. The former group tended to have worse global neuropsychologic impairment, was more likely to have a prior history of substance abuse, and had significantly higher mortality at follow-up, suggesting that psychotic HIV-AIDS patients had an increased CNS vulnerability [51].

HIV-infected patients with primary psychotic disorders, such as schizophrenia and schizoaffective disorder, may have poor access to HIV care, may present to the emergency and medical inpatient setting with untreated advanced HIV illness, and may be at risk for poor adherence to care, unless provided with comprehensive supportive services including psychiatric treatment, housing, and community case management.

In general, treatment with antipsychotic medication requires awareness of HIV-infected patients' susceptibility to neuroleptic-induced EPS as a result of HIV-induced neuronal damage to the basal ganglia. Movement disorders (acute dystonia, parkinsonism, ataxia) can be seen in advanced HIV disease in the absence of antipsychotic exposure. General recommendations include avoidance of high-potency D2 blocking agents (eg, haloperidol); avoidance of depot neuroleptics; and the consideration that maintenance antipsychotic medication may not be necessary for the complete remission of new-onset or transient psychotic symptoms. Most clinicians prefer the use of atypical antipsychotics in this population.

A literature search on the use of antipsychotic medication in HIV-AIDS revealed six studies published since 1993; these studies described treatment of psychosis occurring in delirious, schizophrenic, and manic patients. Agents reported in the literature include haloperidol (mean dose, 3 mg) [52]; thioridazine (mean dose, 145 mg/day) [36]; molindone (20–180 mg/day) [53]; clozapine (mean dose, 27 mg/day) [54]; risperidone (mean dose, 3.3 mg/day) [55]; and olanzapine (10–15 mg/day) [56]. Haloperidol was reported to have a high incidence of EPS [36] and caution is encouraged with clozapine because of the risk for agranulocytosis and interaction with ritonavir.

Herpes simplex encephalitis

A number of viruses can cause viral encephalitis including HSV [57]. HSV is the etiologic agent for herpes simplex encephalitis (HSE), the most common source of acute viral encephalitis in the United States with an annual incidence of 2000 cases yearly [57,58]. Two principle forms of HSV exist: HSV-1, which typically leads to orolabial lesions; and HSV-2, which is responsible for genital herpes lesions. HSV-2 infections more typically result in aseptic meningitis, whereas HSV-1 causes HSE. HSE is a potentially lethal infection with a mortality rate of up to 70% if left untreated and 25% to 30% with treatment [57,59]. Half of HSE cases occur in people over the age of 50, whereas a third of cases are in people under 20 years of age [60].

Clinically, HSE often presents with acute onset of symptoms, such as fever, altered mental status, seizures, and focal neurologic signs, such as aphasia and hemiparesis. Without treatment, patients may progress to coma [58]. Before the acute presentation, there may be a prodrome characterized by headache, fatigue, mild fever, and irritability. Although the mechanisms for pathogenesis in humans are unknown, HSV-1 infection most commonly

affects the lateral temporal cortices and the orbitofrontal and medial temporal regions. Involvement is often bilateral, although asymmetric.

HSE leaves up to 80% of people who survive infection with a number of residual cognitive and neuropsychiatric sequelae [57]. Cognitively, patients may experience significant limitations in anterograde memory formation with additional impairment in retrograde memory. The cognitive effects of HSE are dependent on the sites of the brain involved. Although HSV-1 infection is often bilateral, impairments seen clinically may be dependent on lateralization of HSV-1–related brain injuries. In particular, right hemispheric involvement often leads to subtle deficits with less functional impairment. Left hemispheric neuronal damage, however, creates difficulties in language function and verbal memory [57]. Additional impairments, such as semantic aphasia or mutism, are found in up to 46% of patients with HSE and, more rarely, auditory agnosia has also been documented [57,58]. Long-term consequences of HSE include memory impairment and behavioral and personality changes [57]. Neuropsychiatrically, patients may exhibit symptoms of aggression and disinhibition consistent with a Klüver-Bucy syndrome. Early treatment may ameliorate some of these symptoms; however, particularly in the young and old, cognitive impairments secondary to HSE may lead to postencephalitic dementia [57].

HSE is diagnosed using a combination of clinical features and laboratory and imaging findings (Table 3). Noncontrast CT imaging demonstrates abnormalities in up to 50% of scans including a midline shift. MRI, however, remains the most sensitive imaging tool in diagnosing HSE and is recommended as the first diagnostic step after the clinical examination [58]. MRI findings include focal hyperintensities on T2-weighted imaging. Electroencephalography (EEG) may also be used and initially may show some generalized or focal slowing over the temporal lobes (sites that are commonly a focus for HSV-1 infection), but may change to lateralized, epileptiform activity [57]. Lumbar puncture may demonstrate an elevated opening pressure, CSF leukocytosis, and xanthochromia in addition to a normal CSF glucose level. Polymerase chain reaction demonstrates the presence of HSV-1 infection in the CSF.

HSE is treated with intravenous acyclovir. Recovery is determined in part by how quickly treatment is begun, with increased morbidity and mortality associated with delays in treatment [60]. Although acyclovir treatment of HSV infection in HSE is widely accepted, there is no well-defined treatment specific for the cognitive and neuropsychiatric symptoms associated with HSE. It has been proposed that using dopamine antagonists in a carefully monitored manner may be useful in treating the behavioral disturbances associated with HSE in the acute period. This is based on evidence from an animal study suggesting activation of the mesostriatal dopamine system in HSE. Other treatments used in clinical practice for the neurobehavioral sequelae of HSE include anticonvulsants, benzodiazepines, antipsychotics, stimulants, and cholinesterase inhibitors [57].

Table 3
Clinical features and diagnosis of non-HIV infectious diseases with neuropsychiatric manifestations

Disease	Signs	Focal	CT/MRI	Laboratory tests	Neuropsychiatric sequelae	Treatment
Herpes encephalitis	Fever Altered mental status Focal neurologic signs Seizures Aggression/ disinhibition Language impairments	Yes	Midline shift T2 focal hyperintensities	EEG Lumbar puncture PCR	Difficulties in language function and verbal memory Semantic aphasia or autism Behavioral and personality changes Klüver-Bucy syndrome	Intravenous acyclovir
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	Age of onset between ages 3 and 11 years OCD or tic disorder symptoms Temporal association between symptoms and group A-hemolytic streptococcal infection	No	Basal ganglia enlargement	Antistreptococcal antibody titers D8/17 B-lymphocyte marker ↑ antibasal ganglia Ab's	OCD or tic disorder symptoms Other movement disorders	Plasma exchange Intravenous Ig ±PCN or azithromycin
Neurocysticercosis	Seizures Agitation Psychosis Focal neurologic signs Depression Dementia	Yes	Ring-enhancing lesions Visualization of scolex in cystic structure	ELISA EITB	Seizures Psychosis-like states Dementia	Antihelmenthic agents: praziquantel, albendazole Steroids Anticonvulsants

Neurosyphilis	General paresis Psychosis Emotional lability Anhedonia Social withdrawal Dementia	No	Lesions correlate to specific deficits	VDRL Rapid plasma regain Fluorescent treponemal antibody-absorption assay Lumbar puncture	Mood disorders Psychosis-like states Behavioral changes: disinhibition Dementia	PCN Ceftriaxone
Creutzfeldt-Jakob disease	Rapidly progressive cognitive decline Extrapyramidal signs, ataxia, myoclonus, dysphagia Akinetic mutism Agitation Psychosis Depression	No	Cortical ribboning Basal ganglia and cortical abnormalities Variant CJD: hyperintensity in pulvinar thalami	EEG: periodic sharp wave complexes Tonsil biopsy for variant Creutzfeldt-Jakob disease 14-3-3 assay	Rapidly progressive dementia Cerebellar signs Visual signs Myoclonus Pyramidal symptoms Extrapyramidal symptoms Akinetic mutism Mood disorders Psychosis-like states	No effective treatment has been identified

Abbreviations: EEG, electroencephalogram; EITB, enzyme-linked immunoelectrotransfer; OCD, obsessive-compulsive disorder; PCN, penicillin; PCR, polymerase chain reaction; VDRL, Venereal Disease Research Laboratory.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Over the last 20 years, there has been mounting evidence for connections between group A β-hemolytic streptococcal infections and the development of neuropsychiatric symptoms. Sir William Osler made the original observation that patients with Sydenham's chorea, a complication of group A β-hemolytic streptococcal infection, also exhibited behaviors consistent with tics and obsessive-compulsive disorder (OCD). Later work demonstrated that as many as 70% to 80% of patients with Sydenham's chorea also have clinical features meeting diagnostic criteria for OCD, particularly in children [61,62]. Based on work with children who exhibited abrupt onset of OCD symptoms or tics following group A β-hemolytic streptococcal infection, the development of these symptoms was linked to an immune system–mediated response to the original infection, termed ''pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections'' (PANDAS) [61,63]. Age of symptom onset is approximately 3 years younger in PANDAS than childhood-onset OCD. Additionally, the abrupt onset and relapsing-remitting pattern of symptoms in PANDAS differs from the more gradual onset and chronic pattern in childhood OCD [62,64]. There may be a heritable component to PANDAS, because children with PANDAS have parents and grandparents with significantly higher rates of streptococcal infection complications, such as rheumatic fever, compared with controls [63].

Diagnostic criteria for PANDAS include (1) age of onset between the ages of 3 and 11 years; (2) meeting criteria for OCD or a tic disorder; (3) episodic severity of symptoms; (4) association with group A β-hemolytic streptococcal infection; and (5) association with neurologic abnormalities, including hyperactivity, tic, or choreoform movements [61,62]. Although resembling childhood-onset OCD, PANDAS is distinguished clinically by a distinct temporal relationship between a group A β-hemolytic streptococcal infection and onset of OCD or tics. To make a more definitive diagnosis (see Table 3), obtaining antistreptococcal antibody titers (including antistreptolysin O and antideoxyribonuclease B antibodies) that rise during a symptomatic exacerbation and fall with symptomatic improvement is often needed. Use of these antistreptococcal antibody titers, however, is complicated by the fact that titers may remain high for months following infection [62]. There is also evidence that antibodies directed against the basal ganglia are found more commonly in patients with PANDAS relative to people with uncomplicated streptococcal infections [65]. This finding may shed further light on PANDAS' pathophysiology given that preliminary MRI suggests basal ganglia enlargement in PANDAS patients [66]. In determining susceptibility to PANDAS, studies have indicated that patients with PANDAS are more likely to also have lymphocytes that are positive for the D8/17 marker. This B-lymphocyte alloantigen marker is also associated

with other streptococcal-related conditions, such as rheumatic fever and Sydenham's chorea, further suggesting an immune basis [61,62].

Ultimately, based on the clinical and diagnostic features of PANDAS, it has been suggested that the pathophysiology of PANDAS is based on the development of an autoimmune reaction in patients who are susceptible (ie, based on family history, immunologic markers). This reaction occurs in response to infection with group A β-hemolytic streptococcus where the immune system inappropriately generates antibodies against epitopes on the basal ganglia that resemble streptococcal antigens through the process of molecular mimicry [62]. The resulting immune-mediated inflammatory process in the basal ganglia then may lead to the clinical features of PANDAS [63].

Treatment of PANDAS has been largely based on immunomodulatory therapies. Notably, significant symptomatic improvements have been demonstrated in patients following use of plasma exchange and intravenous immunoglobulin. In one study, severity of OCD symptoms diminished by 45% to 58% following treatment with either plasma exchange or intravenous immunoglobulin [63,67]. Despite this, immunomodulatory therapies have not been recommended as the routine treatment of PANDAS [62]. Use of antibiotic prophylaxis to prevent neuropsychiatric exacerbations following recurrent streptococcal infections has yielded mixed results. Although one double-blind, placebo-controlled trial found no benefit over placebo in preventing PANDAS exacerbations, another trial found that either penicillin or azithromycin were able not only to lower rates of streptococcal infections but also to decrease symptom exacerbations in PANDAS patients [68,69].

Neurocysticercosis

Neurocysticercosis (NCC) is the most common parasitic disease of the nervous system, particularly in developing countries in Asia, Latin America, and Africa. Because of rising rates of immigration from areas where it is more prevalent, however, NCC is appearing more frequently in North America and Europe. Annually, more than 50,000 deaths worldwide are attributable to NCC. Even more patients are left alive with chronic, irreversible brain damage. Moreover, NCC is the major etiology for acquired epilepsy in endemic areas [70]. NCC is caused by infection with the tapeworm *Taenia solium*. Humans are the definitive host for *T solium*, whereas pigs serve as the intermediate host. NCC results generally from fecal-oral transmission where people ingest the eggs of the tapeworm from contaminated food or water. Commonly, this route of transmission occurs through handling of food by others already infected or from improperly cleaned food. Autoinfection also occurs, albeit less frequently [62]. Once in the intestine, the eggs hatch and migrate throughout the body by way of the bloodstream, ultimately depositing into various tissues where they develop into the larval cysticercus form. When the site of larval deposition is in

the CNS, NCC develops. Symptoms of NCC are dependent on the area and extent of nervous system involvement. The four main types of NCC are (1) parenchymal, (2) subarachnoid, (3) ventricular, and (4) spinal [62].

Neurologically, seizures are the most common manifestation of NCC, occurring in 70% of infected patients, especially in the parenchymal form of the disease. The seizures are typically simple partial or generalized tonic-clonic, although patients may also present with focal neurologic deficits based on the sites of infection. Stroke, intracranial hypertension, hydrocephalus, meningeal inflammation, fibrosis, or cyst formation may also occur [70,71]. As a result, NCC is on the differential diagnosis of most neurologic disorders in endemic regions [71].

Given the varied neurologic presentations of NCC, it is not surprising that NCC also has many different psychiatric manifestations. Up to 15% of people infected with NCC exhibit only psychiatric sequelae [71]. In a study examining rates of *T solium* infection among chronic psychiatric inpatients in a community in Venezuela, 18.5% of the inpatients were infected versus 1.6% of controls [72]. Commonly, patients present with acute psychiatric decompensation [62], mimicking psychotic states, such as schizophrenia. In one case report, NCC was marked by acute psychosis characterized by agitation, thought disorganization, paranoia, and auditory-visual hallucinations [70,73]. Other psychiatric manifestations of NCC include depression or dementia; suspicion for NCC-related dementia ought to be high if it occurs in patients who are younger, also have a history of seizures, have acute onset of symptoms, and are from an area where NCC is endemic [62].

The diagnosis of NCC is often difficult because the symptoms of NCC often resemble those from a broad differential of other disorders (see Table 3). NCC most commonly is diagnosed, however, from clinical history, imaging, and laboratory techniques. Besides biopsies that often prove difficult to do, brain imaging using CT and MRI scans allows for visualization of lesions from *Taenia* infection. In active disease, ring-enhancing lesions are most typically seen; visualization of the parasite's scolex within a cystic structure is pathognomonic for NCC [70]. Infection outside the brain parenchyma makes visualization more difficult [62]. Laboratory studies are often used to confirm the diagnosis by investigating patient serology for antibodies related to *Taenia* infection. ELISA and enzyme-linked immunoelectrotransfer are often used for antibody detection [62].

NCC treatment has been controversial with few rigorous, large-scale studies conducted examining the various treatment options. The location of cysts, degree, size and severity of local inflammation around lesions, and symptom severity all affect the treatment choice. This is complicated by findings that the treatments themselves may exacerbate the already present inflammatory response leading to symptomatic worsening [74]. Nevertheless, NCC has been treated for over 20 years using antihelminthic agents, such as praziquantel and albendazole [62,70,74]. Other agents may be given in concert with these drugs including steroids (to treat pericystic

inflammation and NCC-related encephalitis) and anticonvulsants (because of NCC-related seizures). In some instances, surgery may also be needed for placement of ventricular shunts to treat hydrocephalus secondary to arachnoiditis [70,74].

Neurosyphilis

Cases of syphilis have been documented since the late 1400s and, with the HIV epidemic in recent years, have had global resurgence. By the 1920s, more than 20% of patients in American mental hospitals had tertiary neurosyphilis (NS) [75]. With the advent of antibiotics, such as penicillin, the incidence and prevalence of syphilis and resultant NS dropped significantly; however, in parallel with the HIV epidemic, rates of infection (largely by sexual intercourse) began to rise again. There has been an 81% increase in cases of syphilis infection among men since 2000, with an annual incidence of 0.2 to 2.1 cases per 100,000 immunocompetent individuals [75–77]. This has been an important health problem because syphilis facilitates coinfection with HIV [77].

Known as the original ''great imitator,'' syphilis has a number of presentations in virtually all organ systems including the CNS. Consequently, NS has been linked with a diverse array of cognitive and psychiatric syndromes. Untreated, symptomatic NS develops in 4% to 9% of patients infected with syphilis [78].

NS is caused by *Treponema pallidum*, the spirochete responsible for syphilis. Infection may be either symptomatic or asymptomatic. Although NS classically presented with tabes dorsalis or general paresis, these are less common today. Instead, patients with NS are asymptomatic or may present with seizures, ocular symptoms, or with psychiatric and behavioral changes [75]. Early NS may occur within 5 years of infection, whereas late NS (involving the brain parenchyma) typically occurs within 5 to 25 years of infection. HIV infection, however, may accelerate the clinical progression to symptomatic NS [78]. The general paresis form of NS is the type most commonly associated with psychiatric symptoms [75]. The psychiatric presentation of NS typically begins insidiously with mood changes including symptoms of mania or depression. Up to 27% of patients with the general paresis form of NS develop depression characterized by melancholia, suicidal ideation, and psychomotor retardation. Patients may also present with psychosis of acute or insidious onset that may mimic schizophrenia [79]. Personality changes in patients with NS can include emotional lability, antisocial behaviors, anhedonia, social withdrawal, explosive temper, giddiness, hypersexuality, or less attention to personal details. As NS progresses, however, intellectual functioning worsens. Ultimately, symptoms of dementia predominate leading to disability and finally death [75,79]. NS often leads to cortical atrophy and brain lesions. Lesions imaged by MRI in the temporoparietal region have been associated with cognitive impairments

as measured by the Mini Mental-State Examination, whereas lesions in the frontal lobes are associated with overall psychiatric morbidity [80]. Importantly, although prompt treatment of NS is necessary to halt the progression of the illness, it is not expected that patients' mental status will improve completely, because of neuronal loss [75].

Diagnosis of NS is difficult because unlike other infectious organisms, *T pallidum* cannot be grown in culture (see Table 3). Because so many cases of NS are asymptomatic, many infected patients are missed. If the index of suspicion is sufficiently high, however, NS is diagnosed serologically by the rapid plasma regain and Venereal Disease Research Laboratory tests; CSF may be used in the Venereal Disease Research Laboratory assay. If positive, results are confirmed with a microhemagglutination assay for *T pallidum* or with the fluorescent treponemal antibody-absorption assay [75].

NS is treated with a 10- to 14-day course of aqueous penicillin G (18–24 million units/day with 3–4 million units given intravenously every 4 hours). An alternative is to treat the patient with procaine penicillin (2.4 million units daily intramuscularly) combined with probenecid, 500 mg orally, four times daily, particularly if compliant with treatment; ceftriaxone may be used if the patient is allergic to penicillin [75,77]. Sexual partners of the patient may also need evaluation and treatment [75]. There has been little documentation specifically addressing treatment of psychiatric symptoms associated with NS. A recent study by Sanchez and Zisselman [77] recommended use of a typical antipsychotic, haloperidol, or the atypical agents, quetiapine or risperidone, to treat psychosis in NS patients. An anticonvulsant, such as divalproex sodium, was also recommended to address agitation and for mood stabilization [77]. Smaller case reports supported atypical antipsychotics, such as olanzapine and quetiapine, in treatment of NS-associated psychosis [81,82].

Creutzfeldt-Jakob disease

Prion disorders have received much attention in the media given recent epidemics of bovine spongiform encephalopathy (also known as "mad cow disease") and the resulting health risks associated with possible transmission to humans. There are a number of diseases caused by the prion protein, a novel infectious agent composed of a protein ordinarily found in all humans. These diseases are known as "transmissible spongiform encephalopathies" and are found in many mammals including cattle in the form of bovine spongiform encephalopathy; in sheep (known as "scrapie"); and in humans. Prion diseases are believed to occur when the naturally occurring form of the prion protein acquires an abnormal conformational state that facilitates conversion of surrounding prion protein into the pathogenic form, ultimately leading to cell death [83]. In the CNS, this process leads to marked neurodegeneration causing spongiform changes, and consequently, a reactive astrocytosis [84].

Prion disease in humans was first noted in 1920 and 1921 by H.G. Creutzfeldt and A.M. Jacob, respectively [85]. This disease, Creutzfeldt-Jakob disease (CJD), is the most well-known of the human prion diseases, although it is relatively rare with an overall annual incidence of one case per million [83]. Four forms of CJD exist: (1) sporadic CJD, (2) familial CJD, (3) variant CJD, and (4) iatrogenic CJD.

Most CJD cases are sporadic in nature, constituting up to 85% of all reported CJD [83]. Sporadic CJD, similar to the average incidence, has an incidence between 0.5 and 1 per million, although the rate rises to three cases per million among people 65 to 74 years old [85]. In sporadic CJD, the misfolding of the prion protein occurs likely because of a spontaneous mutation in the gene encoding the prion protein. Although the precise significance relating to pathogenesis is unknown, up to 85% of patients with sporadic CJD are homozygote for two copies of the methionine amino acid at codon 129 of the prion protein (Met/Met) [85].

Up to 10% to 15% of CJD cases are familial in origin. Familial CJD is inherited in an autosomal-dominant fashion. Changes in the prion protein involve mutations found in the prion protein (up to 24 individual amino acid substitutions thus far documented) or through insertion of octapeptide repeats [85]. Among the groups with the highest prevalence of familial CJD are Libyan Jews and clusters of families in Chile, Slovakia, Japan, and the United States.

Variant CJD (also known as ''new variant CJD'') was first described in 1996 after a number of CJD cases in the United Kingdom were identified having features that varied from the classic presentation of sporadic CJD. Namely, patients with variant CJD tend to be younger (mean age of 26 years in variant CJD versus 61 years in sporadic CJD); progression of disease is slower (13 months in variant CJD versus 4 months in sporadic CJD); EEG patterns consistent with sporadic CJD may be absent; and psychiatric symptoms are more prominent earlier in the disease progression [85–87]. Significantly, evidence points to the possibility that variant CJD may be caused by eating tissues of cattle infected with bovine spongiform encephalopathy, leaving open the possibility that in the coming years many more people may become ill following exposure to cattle that were unscreened for bovine spongiform encephalopathy before the 1990s. Variant CJD may be also transmissible by blood including transfusions [84,85].

Lastly, iatrogenic CJD has been documented following exposure to tissues from patients infected with CJD or from surgical instruments that have come into contact with those infected. Cases have been reported of patients developing CJD following corneal transplantation or dura mater grafts from infected donors and by cadaveric pituitary growth hormone [85].

Clinically, sporadic CJD presents as a rapidly progressive dementia with average disease duration of only 4 months until death. Moreover, the neurologic and neuropsychiatric symptoms associated with CJD often mimic those found in other dementias, such as Alzheimer's disease or

Lewy body dementia. Common neurologic symptoms may include extrapyramidal signs, cerebellar ataxia, sensory complaints, myoclonus, and dysphagia. In advanced stages of illness, patients can exhibit akinetic mutism and may ultimately die from aspiration pneumonia [83]. Although sporadic CJD was classically believed to present with primarily neurologic manifestations with some psychiatric symptoms appearing late in the course of illness, more recently it has been demonstrated that psychiatric symptoms commonly occur at diagnosis and throughout progression of the disease. Up to a third of cases of sporadic CJD may demonstrate emotional abnormalities and 10% of patients with CJD are hospitalized psychiatrically [88]. In contrast to sporadic CJD, psychiatric and neuropsychiatric symptoms are often the most prominent aspects in the clinical presentation of variant CJD [87].

Psychiatric sequelae of CJD include depressed mood and apathy [89]. A prodromal phase has been described characterized by fatigue, weight loss, impaired sleep, poor judgment, and unusual behavior. Patients may also display unusually intense emotional responses; anxiety; agitation; and psychotic symptoms, such as delusions and hallucinations [87,88]. At times, presentations of primarily depression or psychosis in CJD have made it difficult to distinguish from primary psychiatric disorders and led to misdiagnosis or delays in diagnosis of CJD [90]. Neuropsychologic testing revealed focal cortical deficits in sporadic CJD in contrast to more generalized deficits in variant CJD [91].

Based on criteria suggested by the World Health Organization, definite diagnosis of sporadic CJD involves either neuropathologic examination or detection of the pathogenic scrapie form of the prion protein in brain samples by Western blot (see Table 3) [92]. To receive a probable diagnosis of sporadic CJD patients must have two of the following clinical signs: (1) cerebellar or visual signs; (2) myoclonus, pyramidal, or extrapyramidal signs; or (3) akinetic mutism. Additionally, patients must have detection of the 14-3-3 protein in the CSF or an EEG consistent with CJD coupled with disease duration leading to death in less than 2 years, or investigation not suggestive of an alternative diagnosis [83].

Besides use of clinical symptoms, diagnosis is also based on EEG, imaging, and laboratory findings. Typical EEG findings in sporadic CJD include periodic sharp wave complexes that have either biphasic or triphasic waves or complexes with mixed spikes. In contrast, EEGs of patients with variant CJD do not show periodic sharp wave complexes, but rather have nonspecific slow wave activity [92]. MRI has been used extensively in diagnosis of CJD. There are abnormalities in the basal ganglia and cortex and a unique pattern of "cortical ribboning." Variant CJD patients prominently display a pattern of hyperintensity in the pulvinar thalami [83]. In applying laboratory testing for diagnosis, the detection of the 14-3-3 protein in the CSF of patients with CJD is both quite sensitive and specific for the sporadic form of the disease, although less so in the variant form [93]. A clear diagnosis of

variant CJD may also be made by tonsil biopsy through detection of the scrapie form of the prion protein [94].

Presently, there is no effective treatment for CJD. A focus of potential treatment strategies has been to block accumulation of the pathogenic scrapie form of the prion protein. The antimalarial agent quinacrine and the phenothiazines have been tried with little success in animal and human trials. Another recent approach has been development of vaccines to develop antibodies against the prion protein, although the results of these efforts have been unclear thus far [84].

Lyme disease encephalopathy (neuroborreliosis)

Lyme disease, caused by infection with the tic-borne spirochete *Borrelia burgdorferi*, has been associated with a variety of manifestations, including neuropsychiatric symptoms, or neuroborreliosis. Over the past 20 years, there has been significant controversy regarding the neuropsychiatric manifestations of neuroborreliosis, which is related to the fact that symptoms are often nonspecific (fatigue, sleep disturbance, generalized cognitive complaints, low mood, all symptoms of depression); serologic testing may show evidence of prior systemic exposure but cannot determine whether or not there is acute disease; and symptoms may persist after acute antibiotic treatment [95,96]. Further, the mechanisms of the neuropsychiatric manifestations are not precisely known, being possibly related to direct CNS infection with the organism, to acute or long-term inflammatory processes associated with systemic or CNS infection, or some combination of these. Over the past 10 years, there is accumulating evidence that *B burgdorferi* may adhere to endothelial cells at the blood-brain barrier, causing vasculitis and increased blood-brain barrier permeability, leading to CNS invasion and adherence to astrocytes, resulting in a deleterious inflammatory cascade [97]. The resulting changes in CNS, including abnormalities in subcortical frontotemporal white matter and basal ganglia functioning [98], may explain the more chronic neuropsychiatric symptoms and why antibiotic treatment of these chronic symptoms is generally not associated with improvement in symptoms or CNS pathology [95–97].

In the early stages of acute Lyme disease, patients may present with meningitis, cranial neuritis, and radiculoneuritis [96]. In many such cases, there are positive CSF findings for *B burgdorferi* antibody (IgG) and elevated protein. Cognitive deficits associated with acute and chronic Lyme disease include poor attention and concentration, impaired verbal memory, word-finding difficulties, psychomotor slowing, and executive dysfunction, all consistent with subcortical-frontal pathology. Interestingly, study of Lyme disease patients with chronic cognitive complaints indicates that those with abnormal CSF are more likely than those with normal CSF to have actual neuropsychologic deficits. In those with normal CSF, cognitive complaints are more likely to be associated with concurrent depression [96].

Psychiatrically, patients with both acute and chronic symptoms of neuroborelliosis may present with depression, mood lability, irritability, anxiety, panic attacks, and more rarely, mania, psychosis, and obsessive-compulsive symptoms. There are no large-scale well-controlled studies, however, to suggest that patients with Lyme disease have a greater burden of such symptoms than the general population.

In terms of diagnosis, neurologic examination is usually nonfocal. Bedside cognitive evaluation may be normal to mildly abnormal and more extensive neuropsychologic testing may be necessary to detect the characteristic deficits mentioned previously. Lumbar puncture and CSF evaluation may reveal *B burgdorferi* DNA detected by polymerase chain reaction and antibody to *B burgdorferi*, nonspecific protein elevation, and CSF pleocytosis. The CSF may be normal, however, in a substantial number of cases. Standard structural neuroimaging including brain CT or MRI with contrast is often normal in both the acute and chronic stages of the disease. Quantitative single-photon emission CT of the brain has proved more useful in detecting abnormality, including hypoperfusion in frontal subcortical and cortical regions [98]. This method has been used to follow response to antibiotic treatment.

In terms of treatment, intravenous infusion of ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, has been tested [95]. Other regimens in the literature include intravenous penicillin or a derivative, amoxicillin. Although such regimens have been helpful for neuroborreliosis with clear evidence of abnormal CSF in acute and chronic disease, results have been less favorable in patients with chronic symptoms and minimal objective evidence of CNS infection.

In terms of psychotropic medication treatment for psychiatric comorbidities, the literature is quite sparse. Treatment is generally symptomatic, addressing symptoms of depression (ie, with selective serotonin reuptake inhibitors); fatigue and cognitive complaints (ie, with psychostimulants or modafinil); and mood lability and psychosis (ie, with atypical neuroleptics). Given the subcortical involvement of the spirochete, however, it is important to assess for extrapyramidal side effects with the use of atypical neuroleptic medications.

Summary

This article reviews the clinical characteristics and treatment of a number of infectious diseases that have prominent neuropsychiatric manifestations. Although each entity has unique characteristics, there are several common themes that are important for clinicians to remember. First, maintain an index of suspicion, especially when patients present with new-onset psychiatric symptoms without a history of prior psychiatric illness. It is commonplace to overlook medical or neurologic illness in assuming a primary psychiatric diagnosis. Second, clinicians should take a thorough risk assessment history,

including sexual risk behavior, blood-borne exposures, and travel history. Third, although a thorough diagnostic work-up is necessary to identify and treat the infection, equally important is a full characterization of the psychiatric and cognitive symptoms associated with the infection so as to track the effects of treatment. This becomes particularly important when patients have residual deficits that affect everyday function and ability to work. Finally, it is important to remember that concurrent treatment with antibiotics and psychotropic medications is often necessary. For most of these infectious diseases, formal study of psychotropic medications is relatively infrequent, so clinicians should be vigilant regarding potential drug-drug and drug-disease interactions. Fortunately, when these principles are followed, neuropsychiatric manifestations of infectious diseases can be successfully identified and treated.

References

[1] Fleishman JA, Hellinger FJ. Trends in HIV-related inpatient admissions from 1993–1997: a seven-state study. J Acquir Immune Defic Syndr 2001;28:73–80.
[2] Fleishman JA, Hellinger FH. Recent trends in HIV-related inpatient admissions 1996–2000: a seven-state study. J Acquir Immune Defic Syndr 2003;34:102–10.
[3] Paul S, Gilbert HM, Lande L, et al. Impact of antiretroviral therapy on decreasing hospitalization rates of HI-infected patients in 2001. AIDS Res Hum Retroviruses 2002; 18:501–6.
[4] Cebo KA, Diener-West M, Moore RD. Hospitalization rates in an urban cohort after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2003; 27:143–52.
[5] Ferrando S, Tiamson M. HIV disease. In: Blumenfield M, Strain JJ, editors. Psychosomatic medicine. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 277–96.
[6] Perry S, Tross S. Psychiatric problems of aids inpatients at the New York Hospital: preliminary report. Public Health Rep 1984;99:200–5.
[7] Dilley JW, Ochitill HN, Perl M, et al. Findings in psychiatric consultations with patients with acquired immune deficiency syndrome. Am J Psychiatry 1985;142:82–6.
[8] O'Dowd MA, McKegney FP. AIDS patients compared with others seen in psychiatric consultation. Gen Hosp Psychiatry 1990;12:50–5.
[9] Bialer P, Wallack J, Prenzlauer S, et al. Psychiatric comorbidity among hospitalized AIDS patients vs. non-AIDS patients referred for psychiatric consultation. Psychosomatics 1996;37:469–75.
[10] Ferrando SJ, Rabkin J, Rothenberg J. Psychiatric disorders and adjustment of HIV and AIDS patients during and after medical hospitalization. Psychosomatics 1998;39:214–5.
[11] American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type-1 (HIV-1) infection. Neurology 1991;41:778–85.
[12] Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69:1789–99.
[13] Sacktor NC, Bacellar H, Hoover DR, et al. Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. J Neurovirol 1996;2:404–10.
[14] Wilkie FL, Goodkin K, Eisdorfer C, et al. Mild cognitive impairment and risk of mortality in HIV-1 infection. J Neuropsychiatry Clin Neurosci 1998;10:125–32.
[15] Tozzi V, Balestra P, Serriano D, et al. Neurocognitive impairment and survival in a cohort of HIV-infected patients treated with HAART. AIDS Res Hum Retroviruses 2005;21:706–13.

[16] Anthony IC, Bell JE. The neuropathology of AIDS. Int Rev Psychiatry 2008;20:15–24.
[17] Smit TK, Brew BJ, Tourtellotte W, et al. Independent evolution of human immunodeficiency virus (HIV) drug resistance mutations in diverse areas of the brain in HIV-infected patients, with and without dementia, on antiretroviral treatment. J Virol 2004;78:10133–48.
[18] Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 2008;65:65–70.
[19] Sacktor N, Lyles RH, Skolasky R, et al. HIV-associated neurologic disease incidence changes: multicenter AIDS Cohort Study, 1990-1998. Neurology 2001;56:257–60.
[20] Filippi C, Sze G, Farber SJ, et al. Regression of HIV encephalopathy and basal ganglia signal intensity abnormality at MR imaging in patients with AIDS after the initiation of protease inhibitor therapy. Radiology 1998;206:491–8.
[21] Sacktor N, Skolasky RL, Ernst T, et al. A multicenter study of two magnetic resonance spectroscopy techniques in individuals with HIV dementia. J Magn Reson Imaging 2005;21: 325–33.
[22] Tozzi V, Balestra P, Galgani S, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. AIDS 1999;13:1889–97.
[23] Ferrando SJ, Rabkin JG, van Gorp WG, et al. Longitudinal improvement in psychomotor processing speed is associated with potent combination antiretroviral therapy in HIV-1 infection. J Neuropsychiatry Clin Neurosci 2003;15:208–14.
[24] Ferrando S, van Gorp W, McElhiney M, et al. Highly active antiretroviral treatment (HAART) in HIV infection: benefits for neuropsychological function. AIDS 1998;12:F65–70.
[25] Robertson KR, Smurzynski M, Parsons T, et al. The Prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 2007;21:1915–21.
[26] Hinkin CH, Hardy DJ, Mason KL, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status and substance abuse. AIDS 2004;18(Suppl 1):S19–25.
[27] van Gorp WG, Rabkin JG, Ferrando SJ, et al. Neuropsychiatric predictors of return to work in HIV/AIDS. J Int Neuropsychol Soc 2007;13:80–9.
[28] Perry S, Jacobsberg LB, Fishman B, et al. Psychiatric diagnosis before serological testing for the human immunodeficiency virus. Am J Psychiatry 1990;147:89–93.
[29] Williams JBW, Rabkin JG, Remien RH, et al. Multidisciplinary baseline assessment of homosexual men with and without human immunodeficiency virus infection II. Standardized clinical assessment of current and lifetime psychopathology. Arch Gen Psychiatry 1991; 48:124–30.
[30] Crone C, Gabriel GM. Comprehensive review of hepatitis C for psychiatrists: risks, screening, diagnosis, treatment and interferon-based therapy complications. J Psychiatr Pract 2003;9:93–110.
[31] Maxwell S, Scheftner WA, Kessler HA, et al. Manic syndrome associated with zidovudine treatment. JAMA 1988;259:3406–7.
[32] Brouillette MJ, Chouinard G, Laloonde R. Didanosine-induced mania in HIV infection. Am J Psychiatry 1994;151:1839–40.
[33] Foster R, Taylor C, Everall IP. More on abacavir-induced neuropsychiatric reactions. AIDS 2004;18:2449.
[34] Morlese JF, Qazi NA, Gazzard BG, et al. Nevirapine-induced neuropsychiatric complications, a class effect of non-nucleoside reverse transcriptase inhibitors? AIDS 2002;16:1840–1.
[35] Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in treatment of HIV-1 infection in adults. Study 006 team. N Engl J Med 1999;341:1865–73.
[36] Chen F, Day SL, Metcalfe RA, et al. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. Medicine (Baltimore) 2005;84:98–106.
[37] Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. Clin Infect Dis 2001;33:857–64.

[38] Mayo J, Callazos J, Martinez E, et al. Adrenal function in the human immunodeficiency virus-infected patient. Arch Intern Med 2002;162:1095–8.
[39] Mierlak D, Leon A, Perry S. Does physical improvement reduce depressive symptoms in HIV-infected medical inpatients? Gen Hosp Psychiatry 1995;17:380–4.
[40] Rabkin JG, Williams JB, Remien RH, et al. Depression, distress, lymphocyte subsets and human immunodeficiency virus symptoms on two occasions in HIV-positive homosexual men. Arch Gen Psychiatry 1992;48:111–9.
[41] Ferrando SJ, Goldman JG, Charness W. SSRI treatment of depression in symptomatic HIV infection and AIDS: improvements in affective and somatic symptoms. Gen Hosp Psychiatry 1997;19:89–97.
[42] Holmes VF, Fernandez F, Levy JK. Psychostimulant response in AIDS-related complex patients. J Clin Psychiatry 1989;50:5–8.
[43] Wagner GJ, Rabkin R. Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. J Clin Psychiatry 2000;61:436–40.
[44] Breitbart W, Rosenfeld B, Kaim M, et al. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med. 2001;161:411–20.
[45] Rabkin JG, McElhiney M, Rabkin R, et al. Modafinil treatment of fatigue in HIV+ patients. J Clin Psychiatry 2004;65:1688–95.
[46] Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231–7.
[47] Mijch AM, Judd FK, Lyketsos CG, et al. Secondary mania in patients with HIV infection: are antiretrovirals protective? J Neuropsychiatry Clin Neurosci 1999;11:475–80.
[48] Tanquary J. Lithium neurotoxicity at therapeutic levels in an AIDS patient. J Nerv Ment Dis. 1993;181:518–9.
[49] Halman MH, Worth JL, Sanders KM, et al. Anticonvulsant use in the treatment of manic syndromes in patients with HIV-1 infection. J Neuropsychiatry Clin Neurosci 1993;5: 430–4.
[50] McDaniel JS, for the Working Group on HIV/AIDS. Practice guideline for the treatment of patients with HIV/AIDS. Am J Psychiatry 2000;157:1–62.
[51] Sewell DD, Jeste DV, Atkinson JH, et al. HIV-associated psychosis: a study of 20 cases. San Diego HIV Neurobehavioral Research Center Group. Am J Psychiatry 1994;151: 237–42.
[52] Sewell DD, Jeste DV, McAdams LA, et al. Neuroleptic treatment of HIV-associated psychosis. HNRC group. Neuropsychopharmacology 1994;10:223–9.
[53] Fernandez F, Levy JK. The use of molindone in the treatment of psychotic and delirious patients infected with the human immunodeficiency virus. Case reports. Gen Hosp Psychiatry 1993;15:31–5.
[54] Lera G, Zirulnik J. Pilot study with clozapine in patients with HIV-associated psychosis and drug-induced parkinsonism. Mov Disord 1999;14:128–31.
[55] Singh AN, Golledge H, Catalan J. Treatment of HIV-related psychotic disorders with risperidone: a series of 21 cases. J Psychosom Res 1997;42:489–93.
[56] Meyer JM, Marsh J, Simpson G. Differential sensitivities to risperidone and olanzapine in a human immunodeficiency virus patient. Biol Psychiatry 1998;44:791–4.
[57] Arciniegas DB, Anderson CA. Viral encephalitis: neuropsychiatric and neurobehavioral aspects. Curr Psychiatry Rep 2004;6:372–9.
[58] Chaudhuri A, Kennedy PGE. Diagnosis and treatment of viral encephalitis. Postgrad Med J 2002;78:575–83.
[59] Hjalmarsson A, Blomqvist P, Sköldenberg B. Herpes simplex encephalitis in Sweden, 1990-2001: incidence, morbidity and mortality. Clin Infect Dis 2007;45:875–80.
[60] Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet 2002;359:507–14.

[61] Pavone P, Parano E, Rizzo R, et al. Autoimmune neuropsychiatric disorders associated with streptococcal infection: Sydenham's chorea, PANDAS, and PANDAS variants. J Child Neurol 2006;21:727–36.
[62] Schneider RK, Robinson MJ, Levenson Jl. Psychiatric presentations of non-HIV infectious diseases: neurocysticercosis, Lyme disease, and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection. Psychiatr Clin North Am 2002;25:1–16.
[63] Swedo SE. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Mol Psychiatry 2002;7:S24–5.
[64] Perlmutter SJ, Garvey MA, Castellanos X, et al. A case of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Am J Psychiatry 1998;155: 1592–8.
[65] Pavone P, Bianchini R, Parano E, et al. Anti-brain antibodies in PANDAS versus uncomplicated streptococcal infection. Pediatr Neurol 2004;30:107–10.
[66] Giedd JN, Rapoport JL, Garvey MA, et al. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. Am J Psychiatry 2000; 157:281–3.
[67] Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 1999;354:1153–8.
[68] Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry 1999; 45:1564–71.
[69] Snider LA, Lougee L, Slattery M, et al. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry 2005;57:788–92.
[70] Del Brutto OH. Neurocysticercosis. Semin Neurol 2005;25:243–51.
[71] Tavares AR. Psychiatric disorders in neurocysticercosis. Br J Psychiatry 1993;163:839.
[72] Meza NW, Rossi NE, Galeazzi TN, et al. Cysticercosis in chronic psychiatric inpatients from a Venezuelan community. Am J Trop Med Hyg 2005;73:504–9.
[73] Signore RJ, Lahmeyer HW. Acute psychosis in a patient with cerebral cysticercosis. Psychosomatics 1988;29:106–8.
[74] Nash TE, Singh G, White AC, et al. Treatment of neurocysticercosis: current status and future research needs. Neurology 2006;67:1120–7.
[75] Hutto B. Syphilis in clinical psychiatry: a review. Psychosomatics 2001;46:453–60.
[76] Conde-Sendín MA, Amela-Peris R, Aladro-Benito Y, et al. Current clinical spectrum of neurosyphilis in immunocompetent patients. Eur Neurol. 2004;52:29–35.
[77] Sanchez FM, Zisselman MH. Treatment of psychiatric symptoms associated with neurosyphilis. Psychosomatics 2007;48:440–5.
[78] Carmo RA, Moura AS, Christo PP, et al. Syphilitic meningitis in HIV-patients with meningeal syndrome: report of two cases and review. Braz J Infect Dis 2001;5:280–7.
[79] Sobhan T, Rowe HM, Ryan WG, et al. Unusual case report: three cases of psychiatric manifestations of neurosyphilis. Psychiatr Serv 2004;55:830–2.
[80] Russouw HG, Roberts MC, Emsley RA, et al. Psychiatric manifestations and magnetic resonance imaging in HIV-negative neurosyphilis. Biol Psychiatry 1997;41:467–73.
[81] Taycan O, Uğur M, Ozmen M. Quetiapine vs. risperidone in treating psychosis in neurosyphilis: a case report. Gen Hosp Psychiatry 2006;8:359–61.
[82] Turan S, Emul M, Duran A, et al. Effectiveness of olanzapine in neurosyphilis related organic psychosis: a case report. J Psychopharmacol 2007;21:556–8.
[83] Martindale JL, Geschwind MD, Miller BL. Psychiatric and neuroimaging findings in Creutzfeldt-Jakob disease. Curr Psychiatry Rep 2003;5:43–6.
[84] Caramelli M, Ru G, Acutis P, et al. Prion diseases: current understanding of epidemiology and pathogenesis and therapeutic advances. CNS Drugs 2006;20:15–28.
[85] Pederson NS, Smith E. Prion diseases: epidemiology in man. APMIS 2002;110:14–22.

[86] Spencer MD, Knight RSG, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. BMJ 2002; 324:1479–82.
[87] Wall CA, Rummans TA, Aksamit AJ, et al. Psychiatric manifestations of Creutzfeldt-Jakob disease: a 25-year analysis. J Neuropsychiatry Clin Neurosci 2005;17:489–95.
[88] Moellentine CK, Rummans TA. The varied neuropsychiatric presentations of Creutzfeldt-Jakob disease. Psychosomatics 1999;40:260–3.
[89] Jiang TT, Moses H, Gordon H, et al. Sporadic Creutzfeldt-Jakob disease presenting as major depression. South Med J 1999;92:807–8.
[90] Jadri R, DiPaola C, Lajugie C, et al. Depressive disorder with psychotic symptoms as psychiatric presentation of sporadic Creutzfeldt-Jakob disease: a case report. Gen Hosp Psychiatry 2006;28:452–4.
[91] Kapur N, Abbot P, Lowman A, et al. The neuropsychological profile associated with variant Creutzfeldt-Jakob disease. Brain 2003;126:2693–702.
[92] Wieser HG, Schindler K, Zumsteg D. EEG in Creutzfeldt-Jakob disease. Clin Neurophysiol 2006;117:935–51.
[93] Green AJE. Use of 14-3-3 in the diagnosis of Creutzfeldt-Jacob disease. Biochem Soc Trans 2002;30:382–6.
[94] Collinge J. Molecular neurology of prion disease. J Neurol Neurosurg Psychiatry 2005;76: 906–19.
[95] Kaplan RF, Trevino RP, Johnson GM, et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology 2003;60(12):1888–9.
[96] Kaplan RF, Jones-Woodward L. Lyme encephalopathy: a neuropsychological perspective. Semin Neurol 1997;17:31–7.
[97] Oksi J, Kalimo H, Marttila RJ, et al. Inflammatory brain changes in Lyme borreliosis: a report on three patients and review of literature. Brain 1996;119:2143–54.
[98] Logigian EL, Johnson KA, Kijewski MF, et al. Reversible cerebral hypoperfusion in Lyme encephalopathy. Neurology 1997;49(6):1661–70.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 921–947

CRITICAL
CARE
CLINICS

Psychiatric Aspects of Heart and Lung Disease in Critical Care

Peter A. Shapiro, MD[a,b,*],
David A. Fedoronko, MD[a,b], Lucy A. Epstein, MD[a,b],
Elsa G.E. Mirasol, MD[c], Chirag V. Desai, MD[a,b]

[a]*Department of Psychiatry, Columbia University, 622 West 168 Street, Box 427, New York, NY 10032, USA*
[b]*Consultation-Liaison Psychiatry Service, New York Presbyterian Hospital-Columbia University Medical Center, 622 West 168 Street, Box 427, New York, NY 10032, USA*
[c]*Department of Psychiatry, Veterans Administration Medical Center, 79 Middleville Road, Northport, NY 11768, USA*

Heart and lung diseases are associated with a high prevalence of psychiatric disorders. These psychiatric disorders may occur as premorbid risk factors, as comorbidities, and as complications of the heart and lung conditions. In intensive and critical care settings, appropriate diagnosis and management of psychiatric problems can alter the medical outcome. The most common issues are anxiety, depression, and agitation and delirium. This article addresses differential diagnosis and management, with an emphasis on the intensive care and critical care settings.

Differential diagnosis of anxiety and depression in seriously ill heart and lung disease patients

Although unpleasant feeling states of fear, anxiety, and sadness may be normal responses to stressful and unfortunate life events, not all anxious and depressed moods in patients with new or exacerbated chronic illness are normal reactions to a stressful life event. Depending on diagnosis, some patients who seem to be anxious or unhappy may benefit from reassurance and observation alone, whereas others need additional intervention.

This article is supported in part by the Nathaniel Wharton Fund, New York, NY.
* Corresponding author. Department of Psychiatry, NYPH-CUMC, 622 West 168 Street, Box 427, New York, NY 10032.
E-mail address: pas3@columbia.edu (P.A. Shapiro).

0749-0704/08/$ - see front matter
doi:10.1016/j.ccc.2008.05.003 *criticalcare.theclinics.com*

In general, psychiatric disorders are differentiated from normal mental functioning by the presence of significant subjective distress or impairment in adaptive functioning caused by the mental state itself [1]. This criterion helps to define the set of "adjustment disorders," in which clinically significant emotional distress occurs following a stressful circumstance, and persists for more than a few days, but does not meet criteria for another psychiatric disorder. Adjustment disorders with depressed mood or anxious mood are common in medically ill patients. They often remit spontaneously or in response to brief supportive interventions, such as clarification of the patient's concerns, education about his or her condition, or provision of social support.

More severe depression problems occur in major depressive disorder and bipolar affective disorder. The cardinal feature of major depressive disorder (Box 1) is the presence of a major depressive episode. A major depressive episode is defined by the presence of at least five of the following: persistent depressed mood most of the day; persistent loss of interest in usually enjoyable activities; sleep disturbance; appetite disturbance; difficulty thinking, concentrating, or making decisions; fatigue or loss of energy; inability to experience pleasure; psychomotor retardation or agitation; and thoughts of death or suicidal ideation. Either depressed mood or persistent loss of interest must be included among the features of the episode. The symptoms must persist for at least 2 weeks. Major depressive disorder is defined by the occurrence of a major depressive episode that cannot be better ascribed to another mental disorder or to another medical condition, and is not substance-induced, and in which the symptoms cause significant subjective distress or impairment in functioning. In bipolar affective disorder, significant depressive symptoms may occur, including major depressive episodes, but the patient also has episodes of abnormal, clinically significant mood elevation or irritability (mania or hypomania). In dysthymic disorder, mood symptoms that are below the threshold of a major depressive episode are persistent chronically over at least 2 years. Mood disorders are designated "secondary" when they are attributed to a medical condition, substance, or substance withdrawal. Other mood disorders may occur that do not meet criteria for any of these specific diagnoses because they are below the severity or duration thresholds or have atypical features.

Panic disorder and generalized anxiety disorder are the most common anxiety disorders associated with cardiac and pulmonary diseases. The sine qua non of panic disorder (Box 2) is the occurrence of recurring panic attacks, which are episodes of acute fear or anxiety with abrupt onset and numerous associated physical symptoms, such as shortness of breath, choking sensations, chest discomfort, palpitations, dizziness, lightheadedness, nausea, paresthesias, chills, hot flushes, and sweating, and fears of death, loss of control, or of going crazy; these symptoms are not caused by another medical condition or induced by a substance. They may also be accompanied by a sense of detachment from oneself (ie, depersonalization) or

Box 1. Diagnostic criteria for major depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly caused by a general medical condition, or mood-incongruent delusions or hallucinations.
   (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). **Note:** in children and adolescents, can be irritable mood.
   (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
   (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
   (4) Insomnia or hypersomnia nearly every day.
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   (6) Fatigue or loss of energy nearly every day
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not caused by the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
E. The symptoms are not better accounted for by bereavement (ie, after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, revised. Washington: American Psychiatric Association; 2000.

Box 2. Diagnostic criteria for panic disorder

A. Both (1) and (2):
  (1) Recurrent unexpected panic attacks
  (2) At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
    (a) Persistent concern about having additional attacks
    (b) Worry about the implications of the attack or its consequences (eg, losing control, having a heart attack, ''going crazy'')
    (c) A significant change in behavior related to the attacks
B. Presence or absence of agoraphobia.
C. The panic attacks are not caused by the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism).
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (eg, occurring on exposure to feared social situations); specific phobia (eg, on exposure to a specific phobic situation); obsessive-compulsive disorder (eg, on exposure to dirt in someone with an obsession about contamination); posttraumatic stress disorder (eg, in response to stimuli associated with a severe stressor); or separation anxiety disorder (eg, in response to being away from home or close relatives).

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, revised. Washington: American Psychiatric Association; 2000.

from reality (ie, derealization). In generalized anxiety disorder, the primary feature is persistent nervousness, worry, or fearfulness, associated with fatigue, irritability, restlessness, difficulty concentrating, muscle tension, or sleep disturbance, which continues over a period of months, cannot be controlled, causes distress or impairs function, and is neither caused by a medical condition nor substance-related (Box 3). Secondary forms of these disorders may be caused by medical conditions, as side effects of substances including medications, or as effects of withdrawal from substances.

Psychiatric disorders associated with chronic lung disease

Anxiety symptoms commonly accompany many pulmonary disorders [2]. These have been best studied in chronic conditions, such as asthma and chronic obstructive pulmonary disease [3,4]. The anxiety experienced by

Box 3. Diagnostic criteria for generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (eg, work or school performance).
B. The person finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). **Note:** Only one item is required in children.
   (1) Restlessness or feeling keyed up or on edge
   (2) Being easily fatigued
   (3) Difficulty concentrating or mind going blank
   (4) Irritability
   (5) Muscle tension
   (6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. The focus of the anxiety and worry is not confined to features of an axis I disorder (eg, the anxiety or worry is not about having a panic attack [as in panic disorder], being embarrassed in public [as in social phobia], being contaminated [as in obsessive-compulsive disorder], being away from home or close relatives [as in separation anxiety disorder], gaining weight [as in anorexia nervosa], having multiple physical complaints [as in somatization disorder], or having a serious illness [as in hypochondriasis], and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F. The disturbance is not caused by the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, revised. Washington: American Psychiatric Association; 2000.

affected patients may be described as either generalized anxiety or panic. Some patients with respiratory disease have a combination of both types of anxiety. Patients with acute respiratory failure seem even more anxious that those with stable chronic disease. Most of this increase seems to be panic rather than generalized anxiety [5]. Given the description of a panic attack, there may be some overlap between these symptoms and those of acute respiratory failure. Many patients with acute respiratory failure experience shortness of breath, choking, and chest discomfort. There are others, however, who are overwhelmed by these and the other classic symptoms of panic including fear of dying, losing control, going crazy, depersonalization, or derealization.

Various models have been offered to explain this apparent connection between pulmonary symptoms and the experience of panic (Box 4) [6]. One model involves the psychological theory that some patients are prone to misinterpreting physical sensations within their bodies or "interoceptive cues" that may be associated with dyspnea. These include hyperventilation, chest tightness, tachycardia, and other physical symptoms. They may "catastrophize" the significance of these physical symptoms, leading them to believe that the symptoms are much more dangerous than is actually the case. This misinterpretation escalates their sense of anxiety. This anxiety heightens their focus on and sensitivity to somatic sensations, likely leading them to become even more preoccupied with their physical symptoms. These are again misinterpreted, leading to even more anxiety. This positive feedback cycle continues, leading to a heightened sense of anxiety and even more physical symptoms of panic [7]. Some patients with acute respiratory failure are likely prone to this cycle. For them, the primary issue is fear and the catastrophic misinterpretation of unexpected physical symptoms.

Other models for the connection between acute respiratory failure and panic focus more directly on pulmonary pathophysiology. Various researchers have demonstrated a connection between sodium lactate infusion and the experience of panic symptoms [8,9]. They theorize that the

Box 4. Contributing factors in anxiety associated with lung disease

Catastrophizing cognitions
CO_2 sensitivity
Medication side effects
a. Corticosteroids
b. Methylxanthines
c. β_2-adrenergic agonists
d. Substance abuse (eg, cocaine)
e. Substance withdrawal (eg, alcohol)

metabolism of lactate to carbon dioxide is likely the key in producing panic symptoms. Others have demonstrated a connection between inhalation of exogenous carbon dioxide and the experience of panic symptoms [10,11]. The exact connection between the elevation of carbon dioxide and the development of panic symptoms remains unclear, although some patients are likely more vulnerable to experience anxiety in this setting than others [12]. One theory is that in vulnerable individuals the medullary chemoreceptors are abnormally sensitive to even small increases in carbon dioxide level in the bloodstream. This leads to activation of the locus coeruleus, which leads in turn to autonomic activation [13]. This leads to increased plasma norepinephrine, increased diastolic blood pressure, and an exaggerated ventilatory response, which leads to the symptomatic experience of a panic attack [14]. Patients with acute respiratory failure with resultant changes in blood carbon dioxide levels are vulnerable to experiencing panic symptoms according to this model.

There are likely other factors to consider in patients with acute respiratory failure who are experiencing panic symptoms. Many medications that are used to treat pulmonary disease produce anxiety as a side effect. Corticosteroids are used to treat numerous acute and chronic pulmonary conditions. Their use may contribute to a variety of psychiatric symptoms including anxiety. These side effects are dose-dependent. Some patients experience a spectrum of psychiatric symptoms, with irritability and insomnia at low doses. This may progress to anxiety at moderate doses and psychosis at large doses [15]. Other pulmonary medications are also associated with anxiety. These include β_2-adrenergic agonists and methylxanthines. β_2-Adrenergic agonists frequently cause restlessness, apprehension, anxiety, and tremor [16]. Again, there is a dose and time relationship. Inhaled medications tend to have less of an effect than systemic ones. Methylxanthines are associated with anxiety, fear, and panic [16]. Blood levels may be useful in diagnosing theophylline toxicity. Recreational drug use may also contribute to anxiety experienced by patients with acute respiratory failure during medical hospitalizations. Patients who are acutely intoxicated on stimulants, such as cocaine or amphetamines, often seem very anxious [17]. Others who are withdrawing from sedatives including alcohol, benzodiazepines, barbiturates, or opioids may also seem very anxious [18,19].

Treatment of anxiety in this setting should focus on identification of these possible secondary causes of anxiety. Therapeutic medications, such as steroids, β_2-adrenergic agonists, and methylxanthines, that are contributing to anxiety may be tapered or switched to alternative therapies. Treatment of withdrawal from sedative drugs is also essential, whether these are drugs of abuse or those prescribed for the management of a pre-existing anxiety disorder. There may be some concern about the use of benzodiazepines in the setting of acute respiratory failure. Some benzodiazepines have been shown to decrease patient performance in some pulmonary function tests including forced expiratory volume in 1 second. They also have been shown

to increase P_{CO_2} and decrease responsiveness to carbon dioxide challenge [20]. These may be of significant concern in patients with acute respiratory failure. Some patients with acute respiratory failure seem to benefit from benzodiazepines; however, the literature is mixed regarding efficacy [21,22]. Small doses of short-acting benzodiazepines, such as alprazolam and lorazepam, may be suited to a safe trial in patients with respiratory disease. If the patient is in a closely monitored setting or already requires mechanical ventilation, there may be less need for concern. Antidepressant medications including tricyclics and serotonin reuptake inhibitors seem safe and effective in treating anxiety in patients with respiratory failure [6]. It is generally accepted, however, that these take weeks to achieve a full antianxiety effect; their use in acute respiratory failure is often limited. Buspirone seems safe and may also be effective in relieving anxiety and obsessive symptoms in patients with respiratory failure, but also may take weeks to reach its full effect [23]. Other medications may be used in the acute setting, but these are generally poorly studied regarding safety and efficacy in this patient population. There may be a role for antipsychotics, antihistamines, gabapentin, or pregabalin in select patients.

Nonpharmacologic interventions may also be effective in relieving anxiety. These include controlled breathing exercises, progressive relaxation, guided imagery, hypnosis, biofeedback, and participation in pulmonary rehabilitation [6]. Cognitive behavioral therapy techniques may also be effective. This approach targets anxiety that is caused by the misinterpretation of ''interoceptive cues,'' which leads to the escalating cycle of anxiety and panic. Patients learn to assign new meanings to unexpected and disturbing bodily perceptions. This leads them to feel more confident and in control of their breathing and, consequently, less anxious [24].

Psychiatric factors may play a role in patients who seem difficult to wean from mechanical ventilation. These include delirium, anxiety, and depression. Delirium is characterized by global cerebral dysfunction caused by a patient's medical condition. This manifests as a temporary disturbance in consciousness and cognitive ability (Box 5) [1]. This may make the patient unaware of his or her medical condition or unable to understand or coordinate full participation in the weaning process from mechanical ventilation. Delirium may be related to metabolic disarray as a direct physiologic consequence of pulmonary dysfunction (hypoxia, hypercapnia) or a number of other comorbid medical conditions common in critically ill patients. Isolated hypoxia has been shown to have a significant impact on cognitive function, including loss of judgment, inattention, and motor incoordination with even a slight decrease in oxygenation, and progressing to memory impairment with moderate decrease, and loss of consciousness with significant decrease in oxygenation. Hypercapnia rarely presents in isolation, but is usually accompanied by hypoxia and acidosis. Slight increases in P_{CO_2} cause inattention, forgetfulness, drowsiness, and psychomotor slowing. This may progress to loss of consciousness at significantly increased levels [25]. Other

Box 5. Diagnostic criteria for delirium

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (eg, memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition; or, symptoms developed during substance intoxication or were etiologically related to medication use; or, developed during or shortly after a withdrawal syndrome. (More than one etiology may be present, and in some instances no specific etiology, or a cause other than those listed above, may be identified.)

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, revised. Washington: American Psychiatric Association; 2000.

contributors to delirium must also be considered, and may include other metabolic abnormalities, infections, toxic effects of medications or recreational drugs, and withdrawal from medications or recreational drugs.

Anxiety sometimes interferes with the ability to wean from mechanical ventilation. This anxiety may be directly related to pulmonary pathophysiology. It may be related to side effects of prescribed medications or the rapid tapering of intravenous sedatives. Patients may become physiologically dependent on intravenous sedatives that are used to treat agitation or discomfort associated with mechanical ventilation. If these medications are stopped or tapered too rapidly for a planned weaning trial, significant withdrawal symptoms may occur, including significant anxiety [26].

There are a range of psychologic reactions to mechanical ventilation that may also contribute to a patient's emotional state. One should consider the practical limitations on one's life and experience during mechanical ventilation. Patients may not be able to communicate fully because of tracheal intubation, sedatives, or neuromuscular blockade. It has been reported that the inability to talk is the single greatest contributor to anxiety in mechanically ventilated patients [27]. Associated sleep disruption can intensify

feelings of anxiety. Patients may also experience frightening nightmares. Some report never being able truly to rest. This complaint is supported by studies that have found that the average amount of sleep in ICU patients is as low as 1.8 hours per 24-hour period and that, while sleeping, awakenings from sleep typically occur more than six times per hour, resulting in absence of deep, restorative sleep [28,29]. Pain may be another factor that can have substantial psychologic impact, leading to feelings of anxiety or depression. Loss of independence is a common worry because many patients must depend on others for suctioning, moving, or toileting [30]. Sensory alteration may also be a concern, and this may involve deprivation or overstimulation. Staff or visitors may withdraw from the patient, perhaps because the patient cannot communicate or does not seem alert. Others withdraw because of fear of critical illness or end-of-life issues. Many patients experience sensory overload because of the activity, noise, and light present in the ICU throughout day and night [31].

These factors sometimes limit the patient's fully understanding what mechanical ventilation means to them. For some, it means the conscious and continuous fear of death or disability. For others, it means the loss of independence. They may have the sense that they are entirely dependent on a machine or other people for the most basic bodily functions, and they sense that they have no control. They may not know or trust all of the people involved in their care. Nursing staff may change several times each day. The struggle with independence is a common theme for patients both during mechanical ventilation and at the time of attempted wean.

Patients who only become anxious when weaning is attempted may fear change or have a lack of confidence in the weaning process or themselves. Some fear that they will not be capable of spontaneous breathing after a prolonged period of reliance on the mechanical ventilator. Other emotions commonly experienced are anger, frustration, discouragement, and loneliness [32]. Intervening with these psychologic reactions before attempted weaning may prove effective. Taking time to talk can mitigate patients' anxiety about their limited communication. Allowing the patient to write or use an alphabet or picture board may be helpful. Allowing patients to make choices when possible and keeping them informed of planned procedures and test results may give them more of a sense of control or independence. Continuity of nursing and other care with frequent visits may reduce their sense of isolation or fear of strangers. Frequent orientation and visits with friends and family may address sensory alteration [31]. Many patients have feelings of sadness, but one should also consider the diagnosis of depression in the patient who is difficult to wean. Prospective studies of patient's mood states before attempted weaning have demonstrated increased symptoms of depression compared with controls, cardiac surgery patients, and cancer patients [33]. The connection between mood symptoms and difficulty weaning from mechanical ventilation, however, remains unclear.

In evaluating patients who are difficult to wean from mechanical ventilation, one should evaluate for the presence of delirium, anxiety, and depression. The distinction between these diagnoses can sometimes be challenging and more than one may coexist in the same patient. Delirium may resemble anxiety, especially when the patient is agitated, or depression, especially when the patient is hypoactive. Cognitive testing should be part of the evaluation process. New-onset or fluctuating cognitive deficits or a fluctuating level of arousal or responsiveness are indicative of delirium. Interview should be attempted when sedation has been minimized or discontinued. Feelings of sadness, worthlessness, hopelessness, anhedonia, and wish for death may all support a diagnosis of depression. Reversal of any identified causes of delirium is critical so that the presence of anxiety or depression can be clarified. Once delirium is resolved, patients are much better able actively to participate in the weaning process.

Antipsychotic medication may be effective in managing delirium, especially when the patient is agitated or has psychotic symptoms [34]. Anxiety may be treated with benzodiazepines, such as lorazepam, with due attention to the impact on respiratory status, as previously discussed. If some aspect of anxiety is caused by the rapid taper of intravenous sedatives, these may be replaced with longer-acting oral agents of the same class that can subsequently be tapered at a more gradual pace. Antipsychotic medication may also be effective in the management of anxiety and may present less concern for impact on respiratory status. These too can be added as intravenous sedatives are tapered. The antipsychotic medication can then be tapered over subsequent days as tolerated. Antidepressant medication may play a role in the treatment of patients with severe depression [35], but their benefits may be limited because of the prolonged length of time necessary for them to reach full effect. Because of this, stimulants may be preferred for the treatment of depression in the acute setting. There have been case reports of patients who seemed depressed, had difficulty weaning from mechanical ventilation, and were successfully treated with methylphenidate in doses of 5 to 30 mg/day [36,37]. Nonpharmacologic treatments may also be effective in relieving anxiety and depression in patients on mechanical ventilation, thereby assisting with weaning. These include hypnosis, guided imagery, biofeedback, and music therapy [38].

Psychiatric disorders associated with heart disease

Certain psychologic factors and psychiatric disorders are associated with increased risk for the development of heart disease. A high level of anxiety symptoms, especially phobic anxiety, has been linked particularly to elevated risk of sudden cardiac death, but not nonfatal coronary disease, in large-scale prospective epidemiologic studies [39,40]. High levels of anger and hostility have been linked to increased atherosclerosis, earlier age of onset of clinical coronary disease symptoms, and higher risk of major

adverse cardiac events in patients with diagnosed coronary artery disease, but the strength of the association has been questioned in the face of some negative studies [41–46]. A robust association of previous depressive symptoms and major depressive disorder with incident coronary artery disease (nonfatal myocardial infarction [MI], acute coronary syndromes, cardiac death) has been demonstrated in numerous epidemiologic studies in nonclinical samples; the increase in risk associated with depression has been estimated as approximately 70% [47–49]. ''Negative affect states'' related to depression, including ''vital exhaustion'' and ''type D personality'' (negative affectivity combined with social inhibition) also demonstrate increased risk for coronary artery disease [50–52]. An in-depth review of psychologic factors as risk factors for heart disease is beyond the scope of this article but is available elsewhere [53,54].

The most common psychiatric problems in patients hospitalized for an acute coronary event are anxiety and depression. Patients may not bring these symptoms to the attention of their physicians on their own initiative, and several studies have shown that emotional disturbances are underrecognized in usual cardiac care [55,56]. Early recognition offers opportunity to reduce psychiatric morbidity and may have benefits for cardiac outcomes. Although such symptoms as fatigue, low energy, and sleep and appetite disturbance may discriminate poorly between acute coronary patients with and without clinically meaningful psychiatric problems, other symptoms, such as feeling persistently sad, loss of self-esteem, and feeling unable to experience interest or pleasure about ordinarily pleasurable matters (ie, anhedonia), are effective discriminators of depression [57]. It is probably worthwhile for clinicians caring for patients in acute cardiac care settings to inquire specifically about such symptoms, because they suggest that intervention might be indicated.

Two studies have demonstrated that anxiety in the period immediately after an acute coronary event is associated with adverse cardiac outcomes. Moser and Dracup [58] measured anxiety symptoms with a self-report questionnaire in the first 48 hours of hospitalization in 86 post-MI patients. The rate of in-hospital complications including reinfarction, new-onset ischemia, ventricular fibrillation, sustained ventricular tachycardia, and in-hospital death was 19.6% in patients with anxiety symptoms above the median, compared with 6% for patients with lower levels of anxiety ($P < .01$). Adjusting for other prognostic risk factors, these investigators estimated that anxiety was associated with a 4.9-fold increased relative risk of cardiac complications in the post-MI period. Likewise, Frasure-Smith and colleagues [59] found that a high self-reported anxiety symptom level in 222 post-MI patients was associated with a greater than twofold increased risk of recurrent acute coronary syndromes, even after adjusting for other prognostic factors. Recently, Frasure-Smith and Lesperance [60] extended this observation in a 2-year follow-up study of patients with stable coronary artery disease 2 months after MI. Of 804 subjects, over 5% met criteria for a diagnosis

of generalized anxiety disorder, and over 40% had self-reported anxiety symptoms in the clinically significant range. Major adverse cardiac events in the follow-up period were significantly associated with both generalized anxiety disorder (odds ratio, 2.09; 95% confidence interval [CI], 1.08–4.05) and elevated anxiety symptoms (odds ratio, 1.67; 95% CI, 1.18–2.37).

There have been no large-scale trials directed primarily at treatment of anxiety disorders or high levels of anxiety symptoms specifically in cardiac patients, although some smaller-scale studies suggest that counseling or relaxation training interventions may be beneficial in reducing anxiety outcomes [61–63]. Benzodiazepines (eg, lorazepam), serotonin reuptake inhibitors, and buspirone are generally well-tolerated for pharmacotherapy of anxiety disorders and have little to no cardiovascular effect, other than a tendency to lower heart rate by one to two beats per minute. Drug-drug interactions between serotonin reuptake inhibitors that inhibit the cytochrome P-450 2D6 system and β-adrenergic blockers may exacerbate the negative chronotropic effects of β-blockers [64].

Depression seen in patients after acute coronary events may be a transient adjustment response, but may also be a manifestation of previous history of depressive disorder, continuation of a first episode of depression with onset before the coronary event, or onset of major depression after the coronary event. Major depressive episodes are common, with point-prevalence of about 15%, compared with a lifetime prevalence of 6% to 10% in the general population in the United States [49,65,66]. Moreover, only a minority of major depressive episodes seen in the early aftermath of an acute coronary syndrome quickly remit without intervention [55–57].

Depression after an acute coronary syndrome is associated with a markedly increased risk of recurrent cardiac events and cardiac death, even after adjusting for other prognostic factors [49,65,67]. Frasure-Smith and colleagues [56] demonstrated a greater than threefold increased risk of death over 6-month follow-up associated with major depression immediately after MI. An elevated level of depression symptoms after acute coronary syndromes predicts major adverse events and cardiac mortality up to 5 years after the acute event, in a dose-dependent manner [68–70]. Depression has a similarly negative prognostic impact for patients admitted to hospital for congestive heart failure, whether or not of ischemic etiology [71,72]. Mechanisms mediating these effects of depression and impairing survival include abnormalities in platelet function; autonomic derangements; increased inflammatory activation; and impaired adherence to lifestyle modification (smoking cessation, adherence to medication, exercise, diet modification) (Box 6) [73–76]. Effective treatment of depression after acute coronary syndromes is an important goal.

In this regard, four large trials in recent years have examined treatment of depression in coronary patients. Of these, the SADHART trial, a randomized, placebo-controlled, double-blind trial of sertraline treatment for major depression following admission for acute coronary syndromes, enrolled

Box 6. Possible mechanisms linking depression and coronary disease[a]

A. Physiologic
   1. Platelet activation
   2. Sympathetic nervous system activation
   3. Increased circulating inflammatory factors

B. Behavioral
   1. Smoking
   2. Reduced adherence to medication regimen
   3. Reduced adherence to recommendations for exercise and diet

[a] See text for references.

patients who were still in the hospital, and active medication treatment began within 30 days of the index event [77,78]. In the remaining studies, active treatment began several weeks to several months after a previous coronary event. The SADHART trial showed that sertraline treatment for depression immediately after an acute coronary event (dose range, 50–200 mg/day) had no adverse effect on heart rate, blood pressure, cardiac conduction measures, and left ventricular function, and was not associated with an increase in adverse events, compared with placebo treatment. Sertraline was modestly effective in treatment of depression, particularly for patients with recurrent or more severe depression, or onset of depression before the index cardiac event. These findings suggest that antidepressant treatment with sertraline need not be withheld from patients even early in the post–acute coronary syndrome period. There was no difference in efficacy or safety profile for patients with left ventricular ejection fraction above versus below 30%, suggesting safety in congestive heart failure and in acute coronary syndromes.

The ENRICHD trial, a large randomized trial of a cognitive behavioral psychotherapy intervention in acute post-MI patients with either major depression or a history of major depression and current minor depression, demonstrated that, compared with usual care, a relatively low-intensity intervention (generally, 6–10 psychotherapy sessions over 6 months) was associated with a statistically significant although clinically modest effect on depression symptoms. The intervention had no effect, however, on the study's principal outcome measure, survival free of recurrent MI or cardiac death over 3.5-year (mean) follow-up [79]. Complicating the analysis of the ENRICHD study, some patients with severe depression received sertraline or other antidepressants. Patients who received sertraline had a 42% lower rate of death than patients who did not receive antidepressant therapy, but

because psychopharmacologic treatment was not randomized, the meaning of this finding is uncertain.

In the CREATE trial, 284 patients with stable coronary artery disease and major depression were doubly randomized to receive either interpersonal psychotherapy or clinical management visits without psychotherapy, and to receive the serotonin reuptake inhibitor citalopram or placebo. Citalopram treatment was superior to placebo treatment, whereas interpersonal psychotherapy showed no greater efficacy than clinical management visits in reducing depression symptoms [80]. Citalopram was not associated with a higher rate of adverse events than placebo.

Finally, a European study of post-MI depression intervention (MIND-IT) found significant differences in most depression outcome measures for therapy with the antidepressant mirtazepine compared with placebo [81]. Mirtazepine's safety profile was favorable. Another interesting aspect of this study was the finding that persistence of depression, in comparison with good treatment response, was associated with worse cardiac outcomes at 18-month follow-up: treatment nonresponders had a recurrent event rate (cardiac-related hospitalization or cardiac death) of 25.6%, versus 7.4% for responders. By intention-to-treat analysis, however, a cardiac benefit was not significantly associated with antidepressant treatment [82]. A similar result was noted in the ENRICHD trial [83].

These results leave the field in an unsettled state: treatment of depression after an acute coronary event seems to be at least modestly effective with respect to depression outcome, and recovery from depression seems to be associated with favorable cardiac outcome, yet it remains to be demonstrated that treatment of depression has a favorable effect on cardiac outcome. Still, for the patient in an acute treatment setting, the available data suggest that treatment of depression with either cognitive behavior therapy, citalopram, or sertraline can be undertaken with a reasonable expectation of safety and with the goal of improvement in mood.

Post–coronary artery bypass graft depression

Depressive disorders and elevated depression symptoms are common after coronary artery bypass graft (CABG) surgery, with prevalence of about 15% for depressive disorder at 1 to 2 weeks after surgery, and a substantially higher rate of elevated depressive symptoms [84,85]. These depressive syndromes are associated with increased morbidity and mortality. Major depression at 1 week after CABG surgery was associated with doubled risk of recurrent cardiac events in a 12-month follow-up study of 302 consecutive patients. Depression was as strong a predictor of adverse outcome as low ejection fraction, diabetes, and prior MI [84]. Development of new depression symptoms after surgery, failure to achieve remission of depression symptoms over 6 months after surgery, and severe symptoms were all associated with more mortality in a 5-year follow-up study of over 800 patients [85].

There have been no controlled trials of depression treatment, however, specifically in post-CABG patients. An observational study [86] found that patients undergoing CABG while on SSRI antidepressant therapy actually had worse prognosis than patients not taking antidepressants, but because treatment assignment was not randomized it cannot be determined whether this effect was caused by more severe depression or medical conditions in the treated patients, an adverse effect of the treatment, or another confounding factor.

Post–cardiac surgery delirium and neuropsychologic impairment

Delirium is an acute condition characterized by a waxing and waning disturbance in level of consciousness, reduced awareness of the environment, inability to sustain and focus attention, and impaired cognition, sometimes associated with disorientation, hallucinations, or delusions. Patients may be agitated or hypoactive. By definition, delirium is a direct physiologic consequence of an underlying medical problem, intoxication, or withdrawal (see Box 5) [1]. Delirium occurs in 10% to 50% of cardiac surgery patients, and may be unrecognized, especially in those patients who are not overtly agitated (so-called ''hypoactive'' delirium) [87,88]. Delirium after cardiac surgery is associated with risk of self-harm (eg, because of self-extubation, inappropriate removal of lines, and falls) and with substantially longer length of stay in the ICU and heightened mortality [88–93]. Its prevention and treatment is important for improved outcomes.

Kornfeld and coworkers [94], pioneers in the description of delirium after cardiac surgery, recognized two syndromes, one characterized by confusion immediately on regaining consciousness, and one developing after a so-called ''lucid interval.'' Kornfeld identified the combination of long cardiopulmonary bypass time along with postoperative sleep loss, the combination of sensory overload and sensory monotony, and the absence of clear-cut day and night periods as contributing factors for delirium arising in the ICU after a lucid interval, and recognized that human contact, reassurance, quiet, an opportunity to sleep, and transfer out of the ICU were helpful in many cases. In both forms of delirium, however, Kornfeld recognized the ''organic'' etiology of the disturbance of consciousness. The unfortunate term ''ICU psychosis'' is a misnomer that may have the unintended effect of misleading care providers to attribute delirium solely to the ICU environment, while neglecting the role of toxic, metabolic, infectious, and cerebrovascular etiologic factors.

In contemporary practice, risk factors for delirium in cardiac surgery patients include older age; prior cerebrovascular disease or cognitive impairment; alcohol abuse or dependence; azotemia; hyponatremia; infection; and prolonged sedation with narcotics, benzodiazepines, or propofol. Depression, peripheral vascular disease, and atrial fibrillation are also identified as risk factors in some studies [88,95–98]. In a study of 1267 CABG

surgery patients, patients with low cardiac output in the perioperative period had a significantly greater risk for postoperative delirium [92]. Another large (N = 8139) Scandinavian study of CABG and valve surgery patients, focusing specifically on the development of psychotic symptoms (hallucinations, delusions), identified a similar list of independent risk factors including older age; preoperative renal failure, dyspnea, heart failure, and left ventricular hypertrophy; perioperative hypothermia; and postoperative hypoxemia, low hematocrit, renal failure, hypernatremia, infection, and stroke. ''Off-pump'' surgery was not associated with a lower incidence of delirium [93].

In addition to correction of underlying causes of delirium, treatment of postcardiac surgery delirium often requires use of antipsychotic medication to reduce psychotic symptoms and agitation [64]. Although rigorous clinical trials are lacking, widespread clinical practice embraces the off-label use of a variety of antipsychotic agents including haloperidol, olanzapine (which can be given as an orally disintegrating tablet), and quetiapine, despite the acknowledged metabolic, infectious, and cardiovascular risks of this class of medications. All of these agents have potential to provoke torsade de pointes, although the incidence of this complication is quite low. Parameters to be monitored before and during antipsychotic treatment of delirium should include blood pressure, QTc interval, and potassium and magnesium levels. The prophylactic effect of another antipsychotic medication, risperidone, was tested in a randomized, double-blinded, placebo-controlled study. A total of 126 patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to receive either risperidone, 1 mg, or placebo on regaining consciousness after surgery. The incidence of delirium was 11.1% in risperidone-treated patients versus 31.7% in placebo-treated patients ($P = .009$; relative risk = 0.35; 95% CI, 0.16–0.77) [99]. Aripiprazole, a drug with less propensity for QT prolongation and metabolic side effects, may be a reasonable alternative agent for antipsychotic treatment of delirium [100], but controlled studies have not been reported.

Recent studies indicate that substitution of dexmedetomidine, a centrally acting, selective α_2-adrenergic agonist, for other sedative agents also may substantially reduce the incidence or duration of delirium after cardiac surgery [101–104]. In the early report of Maldonado and coworkers [101], the incidence of delirium after cardiac valve surgery was reduced from 50% to under 5%, and the recent MENDS trial demonstrated a reduction in the incidence of delirium from over 30% to about 10% [104]. In an open trial in 20 cases, introduction of dexmedetomidine facilitated weaning and extubation in 65% of patients who had failed previous weaning trials because of agitation [103]. Problems noted with dexmedetomidine include inadequate sedation, excessive pain, bradycardia, hypotension, and a case of cardiac arrest [105,106]. There are conflicting reports about its use to reduce opioid requirements for pain [107,108].

Chronic neuropsychological impairment may occur after cardiac surgery; prevalence reports vary. In what may be the largest follow-up study, impairment in multiple domains of neuropsychological function was noted in almost half of patients at discharge following surgery, but the prevalence of impairment fell sharply over the next 6 months. The prevalence of impairment was somewhat higher when the same patients were re-examined 5 years after surgery; cognitive impairment at the point of discharge after surgery was a predictor of impairment at 5-year follow-up [109]. The list of risk factors for chronic neuropsychologic impairment after cardiac surgery includes many of the same factors as that for delirium: advanced age, prior neuropsychologic impairment, prior head injury, prior cerebrovascular events including transient ischemic attacks, and history of alcohol abuse or dependence [110,111]. The hoped-for cognitive benefit of ''off-pump'' surgery has not been established [112–114].

Psychiatric complications after left ventricular assist device

In addition to the problems common to cardiac surgery patients in general, patients who undergo implantation of ventricular assist devices experience discomfort and anxiety related to the device. Depending on the specific type of device, noise, the pressure of the device on the stomach, tethering to a machine, and the visible extracorporeal circulation of blood are disturbing features. Once out of the ICU setting, the need to change batteries, master the control panel, and respond to alarms can be cognitively difficult challenges for ventricular assist device patients, many of whom have pre-existing or new neuropsychologic deficits secondary to prior cerebrovascular disease or hypoperfusion, hypoxic episodes, embolic events, or metabolic disarray [111,115]. The ongoing risks of infection, bleeding, and thromboembolic complications (especially stroke) contribute to anxiety associated with ventricular assist device treatment.

Substance withdrawal

Alcohol and benzodiazepine withdrawal is a common problem in the ICU, and often unrecognized, although life-threatening if untreated [19,116]. Alcohol-related medical conditions affect the hospital course of up to 12% to 30% patients in all medical settings [117]. Consequences of alcohol use account for nearly 25% of hospitalizations for traumatic injury, and many of these patients require intensive care [118]. In one study, alcohol use was directly responsible for approximately 20% of all ICU admissions [119].

Withdrawal syndromes can arise from a number of clinical circumstances. Physicians may already be aware of the patient's alcohol use and anticipate withdrawal. Occult alcohol abuse is not uncommon, and it may be diagnosed only when the patient starts to manifest classic symptoms.

Patients may also manifest withdrawal symptoms from known or occult sedative-hypnotic dependence, as from lorazepam or alprazolam. Patients may also withdraw from sedative or anesthetic agents specific to the critical care setting, such as propofol [120]. Last, barbiturate withdrawal may also occur with similar manifestations.

Alcohol, benzodiazepines, and barbiturates all interact with the γ-aminobutyric acid $(GABA)_A$ receptor, a neurotransmitter receptor with a chloride ion channel and several binding sites [121,122]. Benzodiazepines bind to the benzodiazepine site on the $GABA_A$ receptor, which increases the frequency of the chloride channel opening in the presence of GABA [121]. Barbiturates increase the duration of time this channel is open; at high doses, sustained channel opening can occur even in the absence of GABA, which contributes to the substantial lethality risk of barbiturate overdose [121,123,124]. Ethanol also acts as an agonist at the GABA receptor. This common pathway can result in similar behavioral effects, cross-tolerance, and additive properties when used concurrently [125].

Management of alcohol-benzodiazepine withdrawal includes a rapid replenishing of medications that target the GABA receptor. Typically, this involves the administration of benzodiazepine medications at a dose high enough to control the agitation and autonomic response of withdrawal, limited by the need to prevent oversedation and respiratory depression. Many institutions have developed protocols and guidelines for the management of withdrawal syndromes in the ICU, which typically include a stratified system of management with oral or intravenous benzodiazepines [126]. Phenobarbital is also occasionally used in this setting, especially in complicated cases where benzodiazepines have proved ineffective [127]. Adjustments may need to be made for patients with significant liver dysfunction.

Several specific aspects of withdrawal may affect the course of patients with pre-existing cardiopulmonary disease. The autonomic effects of withdrawal, including prolonged hypertension or tachycardia, can precipitate cardiac ischemia, pump failure, and abnormalities in heart rhythm caused by increased myocardial oxygen demand [128]. This is balanced by the tendency of benzodiazepines to cause hypotension, which can also increase cardiac demand by reflex tachycardia. Management of withdrawal can be especially difficult if the patient also requires the use of antihypertensive or cardioprotective agents (eg, β-blockers), because the autonomic manifestations of withdrawal may be masked. Also, there is some evidence to suggest that medications used to treat hypertension, such as nitrates, β-blockers, and calcium channel blockers, have different effects in patients undergoing alcohol withdrawal [129]. During early stages of withdrawal, negative inotropic effects of β-blockers may be reduced, but negative chronotropic effects increased, whereas vasodilator effects of nitrates may be reduced. Antipsychotic medications are necessary at times to address severe agitation associated with withdrawal, despite the risk of adverse cardiac rhythm effects, such as QT prolongation and torsade de pointes [128].

Patients with underlying lung disease have an increased risk of respiratory compromise (because of underlying restrictive or obstructive processes) and may be more difficult to extubate. For these patients, one of the main complications of alcohol withdrawal lies with the benzodiazepine-mediated reduction in ventilatory drive associated with hypoxia, especially at higher doses [128,130].

Children with severe heart and lung disease

Children with heart and lung diseases including bronchopulmonary dysplasia, asthma, cystic fibrosis, α_1-antitrypsin deficiency, congenital heart diseases, familial cardiomyopathy, and acute myocarditis may require critical and intensive care. Intensive and critical care of the pediatric patient requires understanding not only of disease pathophysiology and medical and surgical intervention, but also of the developmental level of the patient. Child psychiatrists are trained to assess the children with regard to their physical, motor, language, cognitive, sexual, and emotional development. In medically ill children, this assessment takes on a greater level of complexity, because there can be a disruption in the normal developmental progression and a regression to more developmentally primitive and at times less adaptive cognitive functioning and coping mechanisms [131,132]. In addition, work with the medically ill child necessitates work with the parents and other significant figures in the child's life. Young children fear separation from their parents, whereas older children and teenagers balance the need for their parents with desires for acceptance into their peer group, a sense of autonomy, and a feeling of mastery of age-appropriate tasks and social roles. At times these desires can overwhelm the ability of the growing child to accept and constructively participate in his or her medical care. Respect for the importance of these normal feelings in the psychological lives of young patients is essential, even in intensive and critical care settings.

Although a comprehensive review is not possible here, the importance of exaggerated anxiety over body image and issues of identity in pediatric heart and lung transplant patients are highlighted. In evaluation of seriously ill children with heart and lung disease for possible transplantation, one is concerned with the patient's degree of understanding of the procedure, based on age, developmental level, and cognitive status; parents, too, must be assessed to ascertain their comprehension of the procedure, and the risks, benefits, and alternatives available, to enable them to make an informed decision. Those providing care must also be mindful of the psychological, social, and emotional resources that the parents are able to contribute in helping the child cope with the transplant process.

Given a particular child's developmental level, his or her conceptualization of illness, body image, and medical procedures can vary tremendously. For example, discussing heart transplantation with a 7 year old is considerably different than with a 15 year old. Each requires a tailored approach,

however, in assessing his or her level of understanding and appreciating developmentally appropriate concerns that may arise. In cases of cardiac transplantation, it is not only young children who can experience magical thinking. Pediatric patients may develop all varieties of fantasy regarding the new heart and what impact it may have on their own thoughts and feelings. Children may fear, in a conscious, literal, and concrete sense, the replacement of their pretransplant identity with the identifying characteristics of the organ donor (eg, language spoken, religious beliefs, emotional attachment to significant others, sex). In older children, anxiety over body image, threats to self-esteem because of the facts of being ill, taking medication, scars and changes in appearance and habitus, and limited ability to participate in school and physical activity, combined with a nearly overwhelming need to fit in with peers, is developmentally typical [133]. Awareness of this constellation of feelings should be helpful in working with young patients and their reactions toward their illness, and may also serve to guide the clinician in anticipating and resolving issues with noncompliance that inevitably arise. One survey estimated that 25% to 40% of pediatric transplant survivors have been found to have some psychiatric issues [134]. Additionally, there are different outcomes based on whether the patient had received the transplant as a result of congenital cardiac disease rather than an acquired cardiac condition [135].

End-of-life care

Physicians who care for chronically and critically ill patients with cardiopulmonary disease routinely confront the challenge of providing both effective and compassionate end-of-life care. This can be further complicated by the presence of psychiatric comorbidities, such as major depression and anxiety. Psychiatrists can assist in the effective management of these patients. This topic is addressed elsewhere in this issue.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. [Text Revision]. Washington, D.C.: American Psychiatric Association; 2000.
[2] Goodwin RD, Pine DS. Respiratory disease and panic attacks among adults in the United States. Chest 2002;122:645–50.
[3] Karajgi B, Rifkin A, Doddi S, et al. The prevalence of anxiety disorders in patients with chronic obstructive pulmonary disease. Am J Psychiatry 1990;147:200–1.
[4] Janson C, Björnsson E, Hetta J, et al. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med 1994;149:930–4.
[5] Yellowlees PM, Alpers JH, Bowden JJ, et al. Psychiatric morbidity in patients with chronic airflow obstruction. Med J Aust 1987;146:305–7.
[6] Smoller JW, Pollack MH, Otto MW, et al. Panic anxiety, dyspnea, and respiratory disease. Am J Respir Crit Care Med 1996;154:6–17.
[7] Clark DM. A cognitive approach to panic. Behav Res Ther 1986;24:461–70.

[8] Pitts FN, McClure JN. Lactate metabolism in anxiety neurosis. N Engl J Med 1967;277: 1329–36.
[9] Cowley DS, Arana GW. The diagnostic utility of lactate sensitivity in panic disorder. Arch Gen Psychiatry 1990;47:277–84.
[10] Van Den Hout MA, Griez E. Panic symptoms after inhalation of CO_2. Br J Psychiatry 1984; 144:503–7.
[11] Papp LA, Klein DF, Martinez J, et al. Diagnostic and substance specificity of carbon dioxide induced panic. Am J Psychiatry 1993;150:250–7.
[12] Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation and panic disorder. Am J Psychiatry 1993;150:1149–57.
[13] Elam M, Yao T, Thorén P, et al. Hypercapnia and hypoxia: chemoreceptor-mediated control of locus coeruleus neurons and splanchnic, sympathetic nerves. Brain Res 1981;222:373–81.
[14] Gorman JM, Fyer MR, Goetz R, et al. Ventilatory physiology of patients with panic disorder. Arch Gen Psychiatry 1988;45:31–9.
[15] Thompson WL, Thompson TL. Use of medications in patients with chronic pulmonary disease. Adv Psychosom Med 1985;14:136–48.
[16] Brunton LL, editor. Goodman & Gilman's the pharmacologic basis of therapeutics. New York: McGraw Hill; 2006. p. 253, 729.
[17] Cox BJ, Norton GR, Swinson RP, et al. Substance abuse and panic related anxiety: a critical review. Behav Res Ther 1990;28:385–93.
[18] Cosci F, Schruers KR, Abrams K, et al. Alcohol use disorders and panic disorder: a review of the evidence of a direct relationship. J Clin Psychiatry 2007;68:874–80.
[19] O'Brien CP. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry 2005;66(Suppl 2): 28–33.
[20] Geddes DM, Rudolf M, Saunders KB. Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide. Thorax 1976;31:548–51.
[21] Mitchell-Heggs P, Murphy K, Minty K, et al. Diazepam in the treatment of the pink puffer syndrome. Q J Med 1980;49:9–20.
[22] Man GC, Hsu K, Sproule B. Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. Chest 1986;90:832–6.
[23] Argyropoulou P, Patakas D, Koukou A, et al. Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease. Respiration 1993;60:216–20.
[24] Brenes G. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. Psychosom Med 2003;65:963–70.
[25] Ropper AH, Brown RH, editors. Adams and Victor's principles of neurology. New York: McGraw-Hill; 2005. p. 964.
[26] Murray MJ, DeRuyter ML, Harrison BA. Opioids and benzodiazepines. Crit Care Clin 1995;11:849–73.
[27] Bergbom-Engberg I, Haljamae H. Assessment of patients' experience of discomfort during respirator therapy. Crit Care Med 1989;17:1068–72.
[28] Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Brit Med J (Clin Res Ed) 1985;290:1029–32.
[29] Friese RS, Diaz-Arrastia R, McBride D, et al. Quantity and quality of sleep in the surgical intensive care unit: are our patients sleeping? J Trauma 2007;63:1210–4.
[30] Johnson MM, Sexton DL. Distress during mechanical ventilation: patient's perceptions. Crit Care Nurse 1990;10:48–57.
[31] Gale J, O'Shanick GJ. Psychiatric aspects of respirator treatment and pulmonary intensive care. Adv Psychosom Med 1985;14:93–108.
[32] Castillo A, Egan H. How it feels to be a ventilator patient. Respiratory Care 1974;19:289–93.
[33] Connelly B, Gunzerath L, Knebel A. A pilot study exploring mood state and dyspnea in mechanically ventilated patients. Heart Lung 2000;29:173–9.

[34] Rea RS, Battistone S, Fong JJ, et al. Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. Pharmacotherapy 2007;27:588–94.
[35] Mendel J, Kahn F. Psychological aspects of weaning from mechanical ventilation. Psychosomatics 1980;21:465–71.
[36] Johnson CJ, Auger WR, Fedullo PF, et al. Methylphenidate in the hard to wean patient. J Psychosom Res 1994;39:63–8.
[37] Rothenhäusler HB, Ehrentraut S, von Degenfeld G, et al. Treatment of depression with methylphenidate in patients difficult to wean from mechanical ventilation in the intensive care unit. J Clin Psychiatry 2000;61:750–5.
[38] Fontaine DK. Nonpharmacologic management of patient distress during mechanical ventilation. Crit Care Clin 1994;10:695–708.
[39] Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994;89:1992–7.
[40] Kawachi I, Sparrow D, Vokonas PS, et al. Symptoms of anxiety and risk of coronary heart disease: the Normative Aging Study. Circulation 1994;90:2225–9.
[41] Barefoot JC, Dahlstrom WG, Williams RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. Psychosom Med 1983;45:59–63.
[42] Shekelle RB, Gale M, Ostfeld AM, et al. Hostility, risk of coronary heart disease, and mortality. Psychosom Med 1983;45:109–14.
[43] Kawachi I, Sparrow D, Spiro A III, et al. A prospective study of anger and coronary heart disease: the Normative Aging Study. Circulation 1996;94:2090–5.
[44] Williams JE, Paton CC, Siegler IC, et al. Anger proneness predicts coronary heart disease risk: prospective Analysis from the Atherosclerosis Risk In Communities (ARIC) study. Circulation 2000;101:2034–9.
[45] Matthews KA, Gump BB, Harris KF, et al. Hostile behaviors predict cardiovascular mortality among men enrolled in the multiple risk factor intervention trial. Circulation 2004; 109:66–70.
[46] Schulman JK, Muskin PR, Shapiro PA. Psychiatry and cardiovascular disease. Focus 2005; 3:208–24.
[47] Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. Epidemiology 1993;4:285–94.
[48] Shapiro PA, Lidagoster L, Glassman AH. Depression and heart disease. Psychiatr Ann 1997;27:347–52.
[49] Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. Am J Psychiatry 1998;155:4–11.
[50] Appels A, Otten F. Exhaustion as precursor of cardiac death. Br J Clin Psychol 1992;31: 351–6.
[51] Denollet J, Sys SU, Brutsaert DL. Personality and mortality after myocardial infarction. Psychosom Med 1995;57:582–91.
[52] Denollet J, Brutsaert D. Personality, disease severity, and the risk of long-term cardiac events with a decreased ejection fraction after myocardial infarction. Circulation 1998; 97:167–73.
[53] Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
[54] Rozanski A, Blumenthal JA, Davidson KW, et al. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol 2005;45:637–51.
[55] Hance M, Carney RM, Freedland KE, et al. Depression in patients with coronary heart disease. Gen Hosp Psychiatry 1996;18:61–5.
[56] Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. JAMA 1993;270:1819–25.
[57] Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. Psychosom Med 1996;58:99–110.

[58] Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? Psychosom Med 1996;58:395–401.
[59] Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Heath Psychol 1995;14:388–98.
[60] Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry 2008;65:62–71.
[61] Bambauer KZ, Aupont O, Stone PH, et al. The effect of a telephone counseling intervention on self-rated health of cardiac patients. Psychosom Med 2005;67:539–45.
[62] Kanji N, White AR, Ernst E. Autogenic training reduces anxiety after coronary angioplasty: a randomized clinical trial. Am Heart J 2004;147:E10.
[63] Lie I, Arnesen H, Sandvik L, et al. Effects of a home-based intervention program on anxiety and depression 6 months after coronary artery bypass grafting: a randomized controlled trial. J Psychosom Res 2007;62:411–8.
[64] Shapiro PA. Heart disease. In: Levenson JL, editor. APPI Textbook of Psychosomatic Medicine. Washington, D.C.: APPI; 2004. p. 423–44.
[65] Shapiro PA. Psychiatric aspects of cardiovascular disease. Psychiatr Clin North Am 1996; 19:613–29.
[66] Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289: 3095–105.
[67] Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med 1999;61:6–17.
[68] Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis following myocardial infarction. Circulation 1995;91:999–1005.
[69] Lesperance F, Frasure-Smith N, Juneau M, et al. Depression and 1-year prognosis in unstable angina. Arch Intern Med 2000;160:1354–60.
[70] Lesperance F, Frasure-Smith N, Talajic M, et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105:1049–53.
[71] Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 2001;161:1849–56.
[72] Faris R, Purcell H, Henein MY, et al. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. Eur J Heart Fail 2002;4:541–51.
[73] Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. Arch Gen Psychiatry 1998;55:580–92.
[74] Carney RM, Freedland KE, Miller GE, et al. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002;53:897–902.
[75] Ziegelstein RC, Fauerbach JA, Stevens SS, et al. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. Arch Intern Med 2000;160:1818–23.
[76] Kronish IM, Rieckmann N, Halm EA, et al. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. J Gen Intern Med 2006;21: 1178–83.
[77] Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.
[78] Glassman AH, Bigger JT Jr, Gaffney M, et al. Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. Arch Gen Psychiatry 2006;63:283–8.
[79] Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing

Recovery In Coronary Heart Disease Patients (ENRICHD) randomized trial. JAMA 2003; 289:3106–16.
[80] Lesperance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (create) trial. JAMA 2007;297:367–79.
[81] Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. Psychosom Med 2007;69:606–13.
[82] de Jonge P, Honig A, van Melle JP, et al. Nonresponse to treatment for depression following myocardial infarction: association with subsequent cardiac events. Am J Psychiatry 2007;164:1371–8.
[83] Carney RM, Blumenthal JA, Freedland KE, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study. Psychosom Med 2004;66:466–74.
[84] Connerney I, Shapiro PA, McLaughlin JS, et al. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. Lancet 2001; 358:1766–71.
[85] Blumenthal JA, Lett HS, Babyak MA, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet 2003;362:604–9.
[86] Xiong GL, Jiang W, Clare R, et al. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. Am J Cardiol 2006;98:42–7.
[87] Mittal D, Majithia D, Kennedy R, et al. Differences in characteristics and outcome of delirium as based on referral patterns. Psychosomatics 2006;47:367–75.
[88] Mirasol EG, Shapiro PA, Fang Y. Delirium in the cardiothoracic ICU: prevalence, predictors, and effect on length of stay. Amelia Island (FL): Academy of Psychosomatic Medicine; 2007.
[89] Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753–62.
[90] Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168:27–32.
[91] van der Mast RC, Roest FH. Delirium after cardiac surgery: a critical review. J Psychosom Res 1996;41:13–30.
[92] Norkiene I, Ringaitiene D, Misiuriene I, et al. Incidence and precipitating factors of delirium after coronary artery bypass grafting. Scand Cardiovasc J 2007;41:180–5.
[93] Giltay EJ, Huijskes RV, Kho KH, et al. Psychotic symptoms in patients undergoing coronary artery bypass grafting and heart valve operation. Eur J Cardiothorac Surg 2006;30: 140–7.
[94] Kornfeld DS, Zimberg S, Malm JR. Psychiatric complications of open heart surgery. N Engl J Med 1965;273:287–92.
[95] Inouye SK, Charpenter PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA 1996;275: 852–7.
[96] Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. Crit Care Clin 2008;24:45–65.
[97] Young J, Inouye SK. Delirium in older people. BMJ 2007;334:842–6.
[98] Kazmierski J, Kowman M, Banach M, et al. Preoperative predictors of delirium after cardiac surgery: a preliminary study. Gen Hosp Psychiatry 2006;28:536–8.
[99] Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007;35:714–9.
[100] Straker DA, Shapiro PA, Muskin PM. Aripiprazole in the treatment of delirium. Psychosomatics 2006;47:385–91.

[101] Maldonado J, Wysong A, van der Starre PJA, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics, in press.
[102] Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother 2007;41: 245–52.
[103] Arpino KA, Kalafatas K, Thompson BT. Feasibility of dexmedetomidine in facilitating extubation in the intensive care unit. J Clin Pharm Ther 2008;33:25–30.
[104] Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644–53.
[105] MacLaren R, Forrest L, Kiser TH. Adjunctive dexmedetomidine therapy in the intensive care unit: a retrospective assessment of impact on sedative and analgesic requirements, levels of sedation and analgesia, and ventilatory and hemodynamic parameters. Pharmacotherapy 2007;27:351–9.
[106] Shah AN, Koneru J, Nicoara A, et al. Dexmedetomidine related cardiac arrest in a patient with permanent pacemaker: a cautionary tale. Pacing Clin Electrophysiol 2007;30: 1158–60.
[107] Corbett SM, Rebuck JA, Greene CM, et al. Dexmedetomidine does not improve patient satisfaction when compared to propofol during mechanical ventilation. Crit Care Med 2005;33:940–5.
[108] Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass surgery: dexmedetomidine-based versus propofol-based sedation regimens. J Cardiothorac Vasc Anesth 2003;17:576–84.
[109] Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001;344:395–402.
[110] Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. N Engl J Med 1996;335:1857–63.
[111] Shapiro PA, Levin HR, Oz MC. Left ventricular assist devices: psychosocial burden and implications for heart transplant programs. Gen Hosp Psychiatry 1996;18:30S–5S.
[112] Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 2000;69: 1162–6.
[113] Van Dijk D, Jansen EW, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 2002;287:1405–12.
[114] Sellke FW, DiMaio JM, Caplan LR, et al. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association Council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research. Circulation 2005;111:2858–64.
[115] Lazar RM, Shapiro PA, Jaski BE, et al. Neurological events during long-term mechanical circulatory support for heart failure: the REMATCH experience. Circulation 2004;109: 2423–7.
[116] O'Brien JM, Lu B, Ali NA, et al. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. Crit Care Med 2007;35:345–50.
[117] Moore RD, Bone L, Geller G, et al. Prevalence, detection, and treatment of alcoholism in hospitalized patients. JAMA 1989;261:403–7.
[118] Blondell RD, Looney SW, Hottman LM, et al. Characteristics of intoxicated trauma patients. J Addict Dis 2002;21:1–12.
[119] Marik P, Mohedin B. Alcohol-related admissions to an inner city hospital intensive care unit. Alcohol Alcohol 1996;31:393–6.
[120] Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care patients. Crit Care Med 1998;26:676–84.

[121] Bateson AN. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. Curr Pharm Des 2002;8:5–21.
[122] Katzung BG, Trevor A. Sedative-hypnotic drugs: examination and board review pharmacology. New York: McGraw-Hill; 1998. p. 171–8.
[123] Morgan WW. Abuse liability of barbiturates and other sedative-hypnotics. Adv Alcohol Subst Abuse 1990;9:67–82.
[124] Zawertailo LA, Busto UE, Kaplan HL, et al. Comparative abuse liability and pharmacological effects of meprobamate, triazolam, and butabarbital. J Clin Psychopharmacol 2003; 23:269–89.
[125] Krystal JH, Staley J, Mason G, et al. Gamma-aminobutyric acid type A receptors and alcoholism: intoxication, dependence, vulnerability, and treatment. Arch Gen Psychiatry 2006;63:957–68.
[126] DeCarolis DD, Rice KL, Ho L, et al. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy 2007;27: 510–8.
[127] Gold JA, Rimal B, Nolan A, et al. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med 2007;35:724–30.
[128] Crippen D. Life-threatening brain failure and agitation in the intensive care unit. Crit Care 2000;4:81–90.
[129] Kahkonen S. Responses to cardiovascular drugs during alcohol withdrawal. Alcohol Alcohol 2006;41:11–3.
[130] Lineaweaver WC, Anderson K, Hing DN. Massive doses of midazolam infusion for delirium tremens without respiratory depression. Crit Care Med 1988;16:294–5.
[131] Pao M, Ballard ED, Raza H, et al. Pediatric psychosomatic medicine: an annotated bibliography. Psychosomatics 2007;48:195–204.
[132] Pao M, Ballard ED, Rosenstein DL. Growing up in the hospital. JAMA 2007;297:2752–5.
[133] Shapiro PA. Life after heart transplantation. Prog Cardiovasc Dis 1990;32:405–18.
[134] Weill CM, Rodgers S, Rubovits S. School re-entry of the pediatric heart transplant recipient. Pediatr Transplant 2006;10:928–33.
[135] Collier JA, Nathanson JW, Anderson CA. Personality functioning in adolescent heart transplant recipients. Clin Child Psychol Psychiatry 1999;4:367–77.

ELSEVIER
SAUNDERS

Crit Care Clin 24 (2008) 949–981

CRITICAL
CARE
CLINICS

Psychiatric Aspects of Organ Transplantation in Critical Care

Andrea DiMartini, MD[a,*], Catherine Crone, MD[b], Marian Fireman, MD[c], Mary Amanda Dew, PhD[d]

[a]*Consultation liaison to the Liver Transplant Program, Starzl Transplant Institute, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213, USA*
[b]*Department of Psychiatry, George Washington University Medical Center, Department of Psychiatry at Inova Fairfax Hospital; Department of Psychiatry Virginia Commonwealth University, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22042, USA*
[c]*Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA*
[d]*Department of Psychiatry, Psychology and Epidemiology; Clinical Epidemiology Program; Research Methods and Biostatistics Core, Advanced Center for Interventions and Services Research in Late Life Mood Disorders; Quality of Life Research, Artificial Heart Program, Adult Cardiothoracic Transplantation, University of Pittsburgh School of Medicine and Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213, USA*

ICU teams are a critical part of the solid organ transplant process. Although kidney transplant recipients usually do not require recovery time in the ICU, virtually all other solid organ recipients receive care from these teams at some point either pretransplantation or posttransplantation. The ICU team is essential in the preparation, stabilization, and recovery of patients undergoing these extraordinary surgical procedures. In addition, transplant recipients may experience medical decompensation requiring ICU treatment years following the initial transplant hospitalization. The psychosocial issues involved during these critical periods of transplantation are important for intensive care physicians and clinicians to understand to provide comprehensive care to transplant patients.

This article was supported in part by R01 DK066266 from the National Institute of Digestive Disorders and Kidney Diseases and R01 MH072718 from the National Institute of Mental Health, Rockville, MD.

* Corresponding author.
E-mail address: dimartiniaf@upmc.edu (A. DiMartini).

doi:10.1016/j.ccc.2008.05.001

This article provides a brief overview of transplant epidemiology, followed by a review of the psychosocial issues relevant to the phases of the transplant process. Considered are the pretransplant evaluation phase, psychiatric disorders in transplant patients, and cognitive impairments and delirium with additional issues specific to particular organs. Also covered is the side effects of immunosuppressive medications and special issues arising with living donors. The relevance of these issues to ICU care is emphasized.

Epidemiology of organ transplantation in the United States

For most organ types the numbers of candidates added to the wait list each year exceeds the numbers receiving transplants (Fig. 1) [1]. In some areas (eg, kidney, liver, lung transplantation) living organ donation has become one option to address the organ shortage (see later section on special issues in living donors). Without an identified living donor, transplant candidates routinely wait for years for an organ, and living donation is not a possibility for all types of transplantation (eg, heart). For all major organ types over 40% of United States wait-listed candidates waited 2 years or more for an organ [2]. Although only 0.5% become medically unsuitable and are removed from the wait-list, 2% refuse transplant after being wait-listed, and 10% to 18% die on the wait-list [2].

Although most transplant candidates are not in the ICU before transplantation, the ICU staff occasionally cares for critically ill transplant candidates on the wait list (see later pretransplant section). For example, the highest transplant status listing for liver and heart transplant candidates is defined as requiring critical care and these patients have the highest priority to receive donated organs. For liver candidates, less than 0.01% is in the highest status (status 1A or B). Less than 10% of heart candidates have the status (status 1A). Of the status 1 liver candidates (fulminant failure not expected to survive 7 days), over 50% receive an organ within a week and 10% die. Of the status

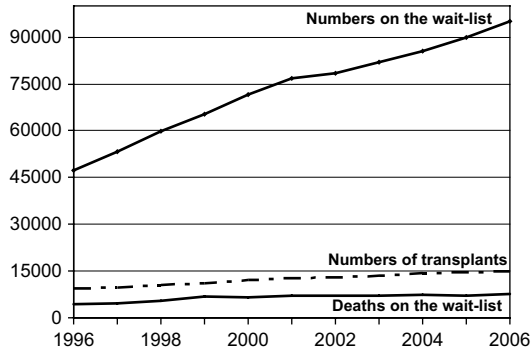

Fig. 1. Waiting list statistics in United States: 1996–2006.

1A heart candidates, 37% are transplanted within 30 days, whereas 11% die within that time [2]. For lung transplant candidates, respiratory failure requiring continuous mechanical ventilation is only a relative contraindication to lung transplantation and the allocation of lungs depends on a complex algorithm of which mechanical ventilation is only one factor.

Following transplantation, recipients of living liver and kidney grafts show the highest long-term survival rates (76% alive 10 years posttransplantation); deceased liver and heart recipients have somewhat lower 10-year survival (59% and 53%, respectively); and lung and intestine recipients have the poorest 10-year survival (41% and 26%, respectively) [2]. These survival statistics are from transplants performed over 10 years ago, however, and advances in technology, immunosuppression, and medical care have improved the survival rates. Graft survival rates can be significantly lower than patient survival rates (eg, 43% for kidney graft survival and 52% for liver graft survival after 10 years), demonstrating that many transplant recipients could face retransplantation 5 to 10 years after their first organ [2] or eventually may require kidney transplantation because of the chronic use of nephrotoxic immunosuppressive medications.

Pretransplant period

Transplant evaluation

The primary goal of a pretransplant psychosocial evaluation is to determine whether a patient has physiologic or psychosocial characteristics that may negatively affect posttransplant outcomes (Box 1). Psychosocial factors include cognitive, behavioral, psychologic, and social issues that may interfere with adjustment to transplantation or ability to adhere to posttransplant medical directives. Many candidates present with at least a few psychosocial issues that require additional attention. Early identification

Box 1. Purpose and goals of a transplant psychosocial evaluation

1. Foster development of individualized treatment plans
2. Establish and strengthen patient-caregiver relationships
3. Encourage patient education and informed consent
4. Evaluate patient coping skills, strengths and weaknesses
5. Assess treatment adherence, barriers to adherence
6. Diagnose psychiatric disorders and give treatment options
7. Identify presence and availability of support system
8. Provide patient with informational and support resources
9. Assist patients and families in developing care plans
10. Participate in team selection of transplant candidates

of these issues during the pretransplant evaluation allows transplant teams the opportunity to develop treatment plans that minimize any negative impact of these factors, while also optimizing patient and caregiver preparedness for transplantation.

In an optimal situation, the psychosocial evaluation consists of a thorough patient interview exploring a variety of issues relevant to transplantation (Box 2). Family members or other caregiving individuals, who help to provide care to the patient following transplantation, may also be interviewed. ICU staff can assist in the pretransplant information gathering process. During their own interviews with patients and families about ICU care they may learn important aspects of how the patient and family are dealing with the immediate stresses and preparing for the future. They may also identify the patient's and family's level of sophistication with medical information. In addition, the ICU staff can provide valuable information about a patient's symptoms and behaviors while in the ICU along with observations about the availability and appropriateness of family and caregiver support. In some cases, the patient is not able to be interviewed and the psychosocial evaluator has to rely solely on other sources (family,

Box 2. Content of a comprehensive psychosocial evaluation

1. History of end-stage organ disease (eg, onset, course, symptomatology)
2. Circumstances leading to transplant referral (expected, emergent)
3. Attitude toward transplantation, level of interest
4. Expectations and concerns regarding transplantation
5. Understanding of transplant process (eg, risks, benefits, long-term)
6. History of treatment adherence (eg, medications, appointments, diet)
7. Past history of other medical problems, experience with illness or hospitalization
8. Current or past psychiatric history, including cognitive functioning and personality disorders
9. Current or past history of substance use or abuse
10. Coping skills, defense mechanisms
11. Family history of medical illnesses and psychiatric illnesses
12. Social history (eg, educational level, employment, living situation)
13. Support system (eg, family, friends, church members, others)
14. Mental status examination

caregivers, medical care providers, and records) to gather relevant information (see cognitive functioning and acute-fulminate organ failure sections).

Acute or fulminant organ failure

Under such conditions as fulminant liver failure or acute cardiomyopathy, patients may require emergent evaluation for transplantation. In these situations, patients often play a minimal role in their evaluation because of the presence of stupor, coma, or mechanical ventilation. Both patients and family members may be overwhelmed with the seriousness of the situation, and the task of having to learn and decide about transplantation.

For patients with fulminant hepatic failure from acetaminophen (representing 96% of transplants because of acute drug-induced hepatotoxicity) [3] or other toxic ingestion or overdose, a thorough psychiatric evaluation is necessary to determine whether the overdose was accidental or intentional. Details regarding the ingestion, prior history of suicide attempts or other self-destructive behaviors, substance abuse, psychiatric disorders, current stressors, and other risk factors for future suicide attempts must be obtained. Many of these patients recover to the point of avoiding transplant, but a small group proceeds on to transplant and require careful consideration about their candidacy.

Decisions to list patients and potential dilemmas

Following completion of the pretransplant evaluation, all information and test results are reviewed, often in a transplant team meeting, to decide whether a patient can be listed for transplantation. For patients with significant psychosocial risk factors, transplant teams may request that additional requirements (eg, addiction counseling, psychiatric treatment, behavioral changes, establishing an adequate support system) be met as a condition to being listed for transplantation. In some cases, patients are not able to complete these requirements because of becoming too ill or they die while attempting to meet candidacy requirements. This is especially likely for patients being evaluated for transplantation while in the ICU. At times, differences in opinion among transplant team members and other health care providers arise regarding a particular patient's candidacy for transplantation. Resolution of these differences requires open discussion among team members and others involved in the patient's care. These discussions not only offer an opportunity to resolve differences, but help to ease the anxiety and discomfort that accompanies declining a patient for transplantation. Additional consultations with medical ethics teams, risk management, and the hospital's legal department may be necessary and instructive with difficult cases (eg, when a candidate or his or her family is challenging candidacy requirements or the candidacy decision of the transplant team). Thorough documentation is essential to delineate the specific issues involved,

expectations of the team for transplantation candidacy, and efforts to work with the patient or family.

Specific coping challenges during the pretransplant period

Waiting period

After patients are listed for transplantation, they may experience a period of elation and relief. Following this, new concerns arise as the realities of the waiting period become evident. Many patients and their families perceive the wait period to be the most psychologically stressful part of the transplant experience. This stress is especially heightened if the candidates are waiting in the ICU. Patients and their families must endure the uncertainty of whether a donor organ will arrive in time and the degree of medical deterioration or loss of functioning the patient will experience before transplantation. For some, health continues a slow decline, whereas others suffer through repeated exacerbations or rapid progression of their disease. Some experience recurrent hospitalizations or prolonged stays in an ICU until a donor organ becomes available. Helping patients to weather the uncertainty of the waiting period requires health care providers to be aware of the stresses unique to this stage of the transplant process.

Preparing for death or maintaining hope

The realization that patients listed for transplantation are also facing terminal illness is often overshadowed by the focus on continued medical care and the pursuit of a donor organ. Patients, families, transplant teams, and other health care providers may overlook or delay discussions on issues relating to end-of-life care, such as living wills, powers-of-attorney, palliative care, and do-not-resuscitate orders [4,5]. Instead, staff energy is often directed at the stabilization and preparation of patients for transplant surgery and postoperative care. Patients and families may resist attempts to address end-of-life issues, partly because of denial. They may also believe that acknowledgment of these issues reflects a sense of hopelessness about transplantation or that the transplant team has become less committed to the pursuit of an organ for them. These concerns can be addressed in collaboration with the transplant team with respect to balancing a hopeful outlook with appropriate acknowledgment of the potential for an undesired outcome [6,7]. Additionally, wait-listed candidates may develop medical contraindications to transplantation (eg, infection, serious stroke or brain damage, hemodynamic instability) and both patient and family should be made aware that their eligibility might change over time for many reasons. By encouraging timely discussion about end-of-life care, patients can also be allowed the opportunity to take an active role in directing their care at a time they are still well enough to do so. Psychologic or spiritual-pastoral counseling may help patients and families negotiate these transitions and prepare them for either transplantation or death.

Patient and family jealousy

During the course of the waiting period, it is not unusual for listed patients to become acquainted with one another during clinic visits and hospital stays. This familiarity can be beneficial to both patients and family members, serving as an additional source of information and support. This can be especially true when the patient is waiting in the ICU and their family members interact with other families in the ICU waiting areas. Nonetheless, this familiarity can become problematic as patients become sicker and the wait for a donor organ more desperate. Inevitably, one patient undergoes transplantation before another, which may raise feelings of jealousy among patients and families still waiting. These feelings may be unexpected, but are understandable in the context of the life-or-death nature of transplantation. In some situations, jealousy may manifest as questions about ranking on the organ wait list, how donor organs are assigned, or body size or blood type requirements. It may emerge in the form of renewed frustrations and fears about the ongoing waiting period [8]. Acknowledging these feelings and answering questions can be beneficial for patients and families, although care must be taken not to share confidential information about other patients.

Psychiatric disorders affecting organ transplant patients

Similar to other medically ill populations, organ transplant candidates and recipients are at elevated risk for significant psychiatric symptoms and diagnosable psychiatric disorders. The development of psychiatric symptoms in transplant patients can reflect the exacerbation of a preexisting disorder or the development of a new-onset disorder. Mood- and anxiety-related disorders are the most common psychiatric illnesses observed both pretransplant and posttransplant, although delirium and cognitive impairment are also often experienced by many transplant patients in the perioperative period. In subpopulations of transplant recipients with histories of substance abuse or dependence (eg, patients with alcoholic liver disease or hepatitis C) the risk for relapse remains a concern both pretransplant and posttransplant. There has been increased recognition that posttraumatic stress disorder (PTSD) may result from traumatic experiences related to the transplant or the ICU stay. There is mounting evidence that each of these classes of psychiatric disorders can affect patient health and psychologic outcomes after organ transplantation.

The ICU staff plays an essential role in the identification of psychiatric symptomatology and psychiatric consultants typically rely on the ICU staff's input about these issues. The ICU staff's round-the-clock observations of the patient's behaviors and affective and cognitive states provide the data from which diagnoses can be made and treatment decided. In addition, their observations of the patient's sleep-wake cycles, physical and motoric activity, appetite, and eating provide evidence of important

neurovegetative symptoms common to many psychiatric disorders. Patient's interactions with family and staff are also important to note. Patients and families may voice concerns to the ICU staff that they may feel reluctant to discuss with the transplant team. These concerns may reveal important aspects of their psychologic and affective states, sense of hopefulness, and their readiness either to pursue transplantation or engage in the posttransplant recovery and rehabilitation process. The following sections review the prevalence, presentation, and issues relevant to psychiatric disorders in transplant populations. Treatment of these disorders is discussed later.

Mood disorders: depression and anxiety

Comorbid psychiatric disorders are common among medically ill transplant candidates: as many as 25% of patients with advanced pulmonary disease, 40% of patients with advanced hepatic disease, and 50% of patients with advanced cardiac disease experience anxiety or depressive disorders [9–11]. Following transplant up to 20% of kidney recipients, 30% of liver recipients, and 63% of heart recipients have been found to develop these disorders especially during the first posttransplant year [12–15]. Some anxiety disorders (eg, panic disorder) seem to be more common both before and after transplantation in patients with end-stage lung disease compared with patients with other types of end-stage organ diseases [14,16,17].

In addition to the multiple psychosocial stressors facing these patients (eg, reduced quality of life, disability, financial pressures), medications and physiologic impairment (eg, electrolyte imbalance, thyroid disorders, and nutritional deficiencies) can produce secondary psychiatric symptomatology. Among patients evaluated for transplantation, many are psychologically worn down by the effects of worsening chronic disease. Others with acute failure may be overwhelmed with the suddenness of their disease and its life-or-death implications. Apathy, fatigue, and memory impairment caused by depression can interfere with a patient's ability or motivation to adhere to a posttransplant regimen of medications, self-monitoring, exercise, and clinic appointments. Excessive or irrational fears caused by an anxiety disorder can cause patients to avoid tests, treatments, hospitals, and other circumstances that raise their level of distress. Anxiety and depression may negatively impact their adjustment to transplantation and early intervention is recommended [17–21].

Patients with depression may manifest symptoms of depressed mood, irritability, loss of interest in activities, changes in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, poor memory and concentration, thoughts of death or suicidal ideation, and feelings of worthlessness or guilt. In a critically ill patient in the ICU, the diagnosis of depression can be challenging because many of these symptoms may also be manifestations of physical illness (Box 3). The presence of anhedonia, guilt, hopelessness, helplessness, and suicidal ideation may be clues that depression is

Box 3. Symptoms and behaviors of anxiety and depression in the medically Ill

Somatic symptoms and behaviors[a]
Fatigue or generalized weakness
Appetite disturbances (anorexia or hyperphagia)
Sleep disturbances (insomnia or hypersomnia)
Increased or excessive physical complaints (out of proportion to the degree of physiologic disturbance)
Psychomotor agitation or retardation
Heightened pain perception
Jitteriness, tremor, sweating
Nausea, gastrointestinal complaints
Chest tightness or palpitations
Shortness of breath or feeling of choking
Dizziness or lightheadedness

Affective and cognitive symptoms and behaviors[b]
Sadness, tearfulness, irritability
Feeling edgy, anxious, overwhelmed
Impaired attention, concentration, memory
Loss of interest, pleasure in enjoyable activities (eg, ability to enjoy visit from family, friends)
Social withdrawal or apathy
Guilt, feeling like a burden to others
Feelings of hopelessness or helplessness
Nightmares, flashbacks, avoidance
Problems with treatment adherence
Heightened vigilance over care needs
Thoughts of death, fears of dying, heightened worries about health
Passive wish for death, suicidal ideation

[a] Somatic symptoms may be attributable to the medical illness or depression or anxiety.
[b] Affective or cognitive symptoms may be clues to presence of depression or anxiety in the setting of severe medical illness.

contributing to the clinical presentation [8]. The presence of persistent irritability, rather than sadness or tearfulness, may also suggest depression. Patients may be reticent to complain of depression during this period of time, feeling ''I should not be depressed'' having just received a life-saving procedure. Medical contributions to depression may include medications, rapid taper of steroids, metabolic derangements, and central nervous system

(CNS) events. Posttransplant complications, changes in family and caregiver dynamics, and the stress of the illness and hospitalization may all contribute. It is important carefully to evaluate the patient with complaints of depression; residuals of delirium, psychotic symptoms, PTSD, anxiety, and cognitive problems may complicate the diagnosis. Families and caregivers may experience symptoms and distress, and the dynamics in their relationship with the patient undergo changes during the transplant process and the focus shifts from one of caregiving to rehabilitation [14,22–25].

Anxiety disorders are also common in transplant patients. Patients with pre-existing anxiety disorders frequently have an exacerbation of symptoms in the transplant setting. Preoperatively patients worry about their health, the outcome of the transplant evaluation, and whether the transplant will actually occur. In the perioperative period, patients and families are anxious as to whether the graft will function, whether complications and graft rejection will occur, and whether the patient will survive and have an improved quality of life. Pretransplant, patients are frequently in denial with regard to the rigors and stressors they face posttransplant. These issues become reality in the perioperative period and patients are particularly vulnerable to anxiety at this time. Anxiety symptoms may increase with the stress of the ICU stay, metabolic derangements, sleep deprivation, postoperative complications, episodes of graft rejection, and medication side effects. Excessive or irrational fears may cause patients to avoid or refuse tests or treatment and be uncooperative with care. Conflicts over daily care, such as the timing of medications, meals, rehabilitation, and tests, can be related to a patient's attempt to control rising fears related to worsening health and an uncertain wait for a donor organ [8]. In evaluating the patient it is important to rule out cardiac arrhythmias, angina, electrolyte imbalances, respiratory distress, seizures, CNS infections, and other CNS pathology as contributing to or causing anxiety symptoms [14,22–26].

Posttraumatic stress disorder

With the onset of medical illness and the need for transplantation patients with pre-existing PTSD from combat experiences or other trauma may experience a recurrence or acute increase in PTSD symptoms. In addition, the life-threatening nature of transplant-related events, transplant surgery, and the ICU stay can cause new-onset PTSD [27,28]. There is increasing evidence that the ICU experience can cause PTSD in a significant percentage of general medical patients, with up to 44% experiencing PTSD symptoms [28,29]. Patients have described vivid flashbacks, severe disturbing nightmares, exaggerated startle responses, and severe anxiety among other symptoms. In a few cases, transplant patients, while delirious, experienced delusions and hallucinations of life-threatening events that led to the development of PTSD [28]. In one study, PTSD experienced during the first year after heart transplantation (but not non-PTSD anxiety symptoms)

predicted mortality during the subsequent 2-year follow-up period [27]. Proactive evaluation, diagnosis, and treatment of anxiety or delirium could lessen symptoms and distress but whether these measures would prevent the onset of PTSD or improve outcomes is not known.

Psychotic disorders

Although it is rare for transplant candidates to have histories of psychotic disorders (ie, schizophrenia, schizoaffective disorder, bipolar disorder), such patients can do well posttransplant if their disorders are well-controlled [30]. These patients should undergo an extensive pretransplant psychiatric evaluation. Information on how they have tolerated prior hospitalizations and specifically ICU stays can help to guide future treatment planning and help the ICU and transplant teams prepare for their ICU stay. Patients with psychotic disorders may experience disturbances in judgment or reality testing when faced with new experiences, multiple stresses, or situations where they lack a sense of control. This is especially true in the ICU where stressors related to the severity of their illness, perceived loss of control, and excessive environmental stimulation may precipitate psychotic symptoms. In this context these patients may become agitated, irritable, delusional, or paranoid. They may experience auditory or visual hallucinations or become uncooperative with their medical care. Although the etiology of their symptoms is linked to their underlying psychiatric disorders, the treatment of these symptoms and behaviors is similar to treatments offered for behavioral symptoms caused by medical decompensation related to end-stage organ failure (eg, hepatic encephalopathy [HE]; see later).

Substance abuse

Whether to offer new organs to patients with substance abuse or dependence disorders has been a source of debate within the transplant community and society at large. Although concerns have been raised over posttransplant relapse and its potential to contribute to nonadherence, eventual graft failure, and patient death, there is little evidence that carefully selected individuals experience high rates of relapse. A recent meta-analysis demonstrated relapse rates as low as 3% to 6% of patients per year among individuals transplanted after histories of alcohol or illicit drug use [31]. Even those on methadone maintenance do not seem to relapse often while remaining on treatment [32].

Transplant teams often expect patients to achieve a certain duration of pretransplant abstinence (often at least 6 months) before they are listed for transplant. Although this may allow for some demonstration of patients' commitment to abstinence, stable abstinence is measured in years and patients in end-stage organ failure may not be able to survive the added wait time. More importantly, patients must gain understanding of and

insight into their addiction and develop healthier coping skills. This often requires participation in formal rehabilitation programs, addiction treatment or 12-step groups, and family education. For patients in the ICU, requirements for addiction rehabilitation and specific periods of abstinence may not be achievable in the time before transplantation. These patients may generate a great deal of emotion and even conflict among team members because personal opinions on these candidates may be very different. Because there is no national policy for these cases, the decision is left to the treating physicians and clinicians and each transplant team must determine the relative importance of these issues with respect to their own policy and selection criteria. Teams should apply their criteria consistently, however, to prevent disagreements over individual cases.

For ICU staff, the care of patients with addictive disorders who need transplantation requires adoption of a well-informed, nonjudgmental stance. Patients with histories of alcohol or benzodiazepine dependence should be monitored for the development of withdrawal symptoms. Many withdrawal syndromes, especially for alcohol, opioids, and sedative hypnotics, present with symptoms of sympathetic hyperactivity (tachycardia, hypertension, hyperthermia). This may complicate transplant management, confuse the diagnostic picture when evaluating medical complications, and result in increased morbidity. Medications may be required to avoid serious complications of withdrawal, such as autonomic instability and seizures. If the patient is alcohol dependent, administration of thiamine may be required to prevent the Wernicke-Korsakoff syndrome. Opioid-dependent patients on methadone maintenance continue to require their outpatient dose of methadone, along with additional opioid medications for treatment of pain [33]. Patients dependent on opioids may have substantial tolerance to these medications and may require higher than expected doses to achieve adequate pain control. Although patients with substance abuse may have comorbid anxiety disorders, treatment of their symptoms requires cautious use of benzodiazepines and optimized use of other psychotropic agents. In addition to medication management, it is equally important to obtain consultation with specialists in addiction and arrange for the patient to receive treatment for the substance use disorder as soon as practical.

Pretransplant organ-specific cognitive disorders and encephalopathy

Cognitive disorders and delirium

Through the pretransplant to posttransplant phases patients frequently experience reductions in cognitive functioning ranging from subclinical or mild symptoms to frank delirium (Table 1). Impairment in cognitive function often results from end-stage organ disease and its physiologic sequelae but may also occur because of other comorbid disease processes (eg, CNS vascular disease from diabetes or hypertension); damage from prior

Table 1
Delirium and other cognitive disorders

Symptoms	Acute delirious state	Mild cognitive disorder or early signs of delirium
Onset	Often rapid	Slow, insidious
Clouding of consciousness	Yes	No
Waxing and waning of alertness	Yes	No or mild
Disorientation	Yes	No or mild
Fluctuation of symptoms over brief periods of time	Yes, often severe	No
Sleep-wake cycle disturbance	Yes, often severe	Possibly present
Increased or decreased psychomotor activity	Yes	No or mild
Sensory misperceptions (illusions, hallucinations)	Sometimes	No
Tangential, rambling, incoherent thought or speech	Sometimes	No
Impaired reality testing or delusions	Sometimes	No
Impaired attention or concentration	Yes, often severe	No or mild
Memory impairment	Yes, both short- and long-term memory affected	Yes, mainly short-term memory affected
Disturbances in executive function-planning, organization, abstraction	Yes, often severe	Yes
Mood or personality changes	Yes	Sometimes

Data from Trzepacz PT. Delirium. In: Levenson J, editor. Textbook of psychosomatic medicine. Washington: American Psychiatric Publishing; 2005. p. 91–130.

exposures (eg, alcohol or drugs); or be the result of prior structural damage (eg, stroke), medication side effect, or head trauma. Before transplantation it is critical to differentiate between the fluctuating course of a delirium, which is potentially reversible, and more persistent cognitive deficits that may represent a pre-existing dementia or a static cognitive impairment. The reversibility or even progression of deficits may in part rely on age; the homeostatic reserve of the brain; prior CNS insults; and the ability to withstand future transplant-related stresses (eg, prolonged anesthesia, use of cardiac bypass, hemodynamic fluctuations, and posttransplant immunosuppressives). Although the restoration of normal organ functioning and

physiology posttransplant may be expected to correct the reversible cognitive impairments, deficits may take months to years to resolve [34].

In heart failure, low cardiac output and CNS hypoperfusion from reduced cerebral blood flow can contribute to cognitive impairments. Impaired cerebrovascular reactivity and ischemia may result, even in the absence of acute cerebrovascular events. Cardiac medications, including inotropic agents, can also contribute to cognitive impairments. CNS microemboli are common in pre–heart transplant patients, especially for those on ventricular assist devices (see section on VADs). In end-stage lung disease, hypoxia and hypercapnia may cause mild to severe cognitive deficits in these patients, particularly in the areas of executive functioning, attention, and memory [35]. Oxygen therapy may improve cognitive functioning in certain candidates and these patients can benefit from lung transplantation but the extent to which these deficits are reversible is unclear [35]. Hepatic and uremic encephalopathies are two specific areas considered in detail later.

Evaluation of delirium during this period of time must include careful medical examination of the patient and review of the medications and laboratory studies (Box 4). Brain imaging, electroencephalogram recording, and lumbar puncture may also provide important information. The differential diagnosis is broad and includes metabolic derangements, infections, and side effects of medications (Boxes 5 and 6) [22]. Environmental attributes can also contribute to the development of delirium. These factors include disruption of the normal day-night cycle with constant stimulation in the ICU, sleep disruption, and lack of orienting cue. To the extent possible, normalization of the sleep-wake cycle should be attempted in the ICU, and waking the patient during the night should be avoided unless necessary. Room lights should be off or dimmed during the night unless they are necessary to provide care to the patient. Frequent reorientation to time and

Box 4. Diagnostic tools to identify cognitive disorders

- Patient and family interview and observations
- Review of medications
- Screening cognitive examinations (MMSE, CAM-ICU, NEECHAM, ICDSC)
- Formal neuropsychologic testing
- Laboratory studies
- Electroencephalogram
- CNS imaging

Data from Trzepacz PT. Delirium. In: Levenson J, editor. Textbook of psychosomatic medicine. Washington: American Psychiatric Publishing; 2005. p. 91–130.

Box 5. Potential causes of delirium in transplant patients

Metabolic
Dehydration
Volume overload
Hypoxia
Electrolyte imbalances
  Hyponatremia, hypernatremia
  Hyperkalemia
  Hypercalcemia
  Hypomagnesemia
Acidosis
Alkalosis

Infectious
Sepsis
Pneumonia
Spontaneous bacterial peritonitis
Abscesses
Cellulitis
Meningitis, encephalitis
Endocarditis

Organ failure
Hepatic encephalopathy
Uremic encephalopathy
CNS hypoperfusion

Medications (see Box 6)
Endocrine
  Hypothyroidism
  Hyperthyroidism

Cerebrovascular
Seizures
Cerebral edema
Cerebrovascular accident, embolic or hemorrhagic
Subdural hemorrhage
Hypertensive encephalopathy

Miscellaneous
Alcohol or drug intoxication and withdrawal states
Autoimmune disorders, vasculitis
Disseminated intravascular coagulation
Fever
Sensory deprivation
Sleep deprivation
Neuroleptic malignant syndrome
Malignant hyperthermia

Box 6. Medications commonly used in transplant patients that may cause delirium

Immunosuppressants
Corticosteroids
Calcinurein inhibitors (tacrolimus, cyclosporine)

Analgesic pain medications
Opioid analgesics
Nonsteroidal anti-inflammatory medications

Antimicrobials
Acyclovir, ganciclovir
Amphotericins
Cephalosporins
Interferon-α
Vancomycin
Aminoglycosides

Anticholinergics
Antihistamines
  Diphenhydramine
  Hydroxyzine
  Benztropine
Atropine
Scopolamine

Tricyclic antidepressants
Amitriptyline
Doxepin

Phenothiazines
Chlorpromazine

Antiemetics and related medications
Proclorperazine
Promethazine
Metoclopramide

Cardiac medications
β-blockers
Clonidine
Digoxin

Sedative-hypnotics
Benzodiazepines (eg, diazepam, lorazepam)
Barbiturates

Miscellaneous
Cimetidine
Ranitidine
Baclofen
Lithium
Stimulants

place and reminding the patient who the staff are who are caring for the patient and why the patient is hospitalized may also be helpful. Breitbart and coworkers [36] noted that delirious patients with perceptual disturbances and severe delusions were more likely to experience later delirium-related distress than those without these symptoms. Whether treatment of delirium can prevent future distress or the development of delirium-related PTSD symptoms is unknown.

Liver disease and hepatic encephalopathy

HE is a specific type of delirium commonly experienced by patients with hepatic dysfunction. Symptoms of HE may be considered on a continuum from subclinical or minimal to overt and severe. In addition to the signs and symptoms that characterize delirium (see Table 1) patients can also have affective-emotional dysregulation; psychosis; behavioral disturbances; bioregulatory disturbances; and disturbances of the motor system including asterixis, tremor, increased deep tendon reflexes, increased muscle tone, ataxic gait, bradykinesia, slurred speech, or incoordination. Patients with HE associated with acute fulminant hepatic failure are at risk for cerebral edema, increased intracranial pressure, seizures, and death pretransplant [37,38]. The prognosis for these patients is poor with or without liver transplant particularly if the intracranial pressure is greater than 40 mm Hg or cerebral perfusion pressure is less than 40 mm Hg [39]. For patients with acute liver failure who experience an acute change in mental status or progress to advanced-stage HE, head CT is recommended to evaluate for cerebral edema or intracranial bleed [40]. Persistent HE is rare but can be observed in patients with extensive portocaval collateral circulation or after surgical or transjugular portosystemic stent shunting procedures [41]. An electroencephalogram may show common abnormalities, such as generalized slowing of dominant rhythm or less commonly nonconvulsive seizures; neuropsychologic testing assessing psychomotor speed, praxis, concentration, and attention is more efficient and perhaps more sensitive in determining minimal HE [38,40,42].

HE most likely has a multifactor pathogenesis. Changes in brain metabolism and disorders of neurotransmission seem to be contributing factors.

Although the predominant treatment strategy is to decrease production and absorption of ammonia in the gastrointestinal tract, it is not the only substance implicated in the pathogenesis of HE. HE can be precipitated by significant protein intake; gastrointestinal hemorrhage (causing increased protein load in the intestine); uremia; use of some psychoactive medications or diuretics; dehydration; or electrolyte imbalance [42,43]. Treatments should be aimed at correcting precipitating factors and should include administration of a nonabsorbable disaccharide (eg, lactulose), which acts as an osmotic laxative to flush out ammonia. Additional treatments include the use of nonabsorbable antibiotics to reduce intestinal bacteria that convert protein to ammonia. A protein-restricted diet may not be feasible for patients with advanced liver disease with the loss of muscle mass and cachexia. Medications that can contribute to symptoms of HE or slow intestinal motility, such as those with anticholinergic activity and opioid analgesics, should be avoided.

Renal disease and uremic encephalopathy

Chronic renal failure results in multiple catabolic, metabolic, and endocrinologic processes that contribute to the development of uremic encephalopathy. The accumulation of neurotoxic substances, such as urea, uric acid, guanidine compounds, hippuric acid, and indoleacetic acid, is believed to contribute to the encephalopathy; no single metabolite has been identified as the sole cause. Other pathophysiologic changes implicated in uremic encephalopathy include hormonal elevations, and electrolyte imbalances including acidosis, hyponatremia, hyperkalemia, hypocalcemia and hypermagnesemia, anemia, malnutrition, and CNS factors, such as increased calcium and decreased γ-aminobutyric acid and glycine activity.

The symptoms of uremic encephalopathy typically fluctuate and can begin insidiously with patients experiencing mild cognitive impairment, irritability, or insomnia. Physical symptoms (eg, slurred speech, muscle twitches, or restless legs) can also occur. Symptoms can progress slowly or rapidly to confusion, lethargy, overt delirium, seizures, psychosis, catatonia, and stupor or coma. An electroencephalogram can aid in the differential diagnosis of encephalopathy, typically showing generalized slowing of the dominant rhythm, versus seizures and nonconvulsive status epilepticus, which can occur in uremia and be mistaken for uremic encephalopathy. Removal of uremic toxins by hemodialysis, correction of electrolyte imbalances and anemia, and the treatment of malnutrition can diminish the symptoms of encephalopathy and improve cognition. Seizures may require treatment with anticonvulsants.

Uremic encephalopathy is also associated with a cliniconeuroradiologic syndrome termed "posterior reversible (leuko)encephalopathy syndrome" (PRES). Characteristic radiographic findings on CT or MRI are seen in the posterior cortical and subcortical white matter. Risk factors for

PRES in renal patients include abrupt changes in blood pressure; autoimmune disorders; thrombotic thrombocytopenic purpura; infections (specifically viral) and sepsis; and nonspecific renal inflammatory conditions (eg, glomerulonephritis, hepatorenal syndrome) [44]. Early recognition allows corrective action to be taken. Action is especially important with respect to severe or unstable blood pressure, which frequently accompanies the syndrome [44]. Prompt treatment may avoid potentially permanent brain damage.

Heart failure and ventricular assist devices

The extreme shortage of donated hearts and the growing list of heart transplant candidates indicates that VAD therapy will play an increasingly significant role in the treatment of end-stage heart disease. Progress in the development of VADs from external or paracorporeal devices to implantable devices has dramatically improved both the physical and psychologic health of patients with end-stage heart failure. Although these devices are primarily used as bridges to transplantation, they can also bridge a patient to recovery (eg, after an acute illness, such as fulminant myocarditis) and are now also offered as ''destination'' therapy for some patients ineligible for transplant. The newest VADs now include implantable left ventricular or biventricular versions that have been miniaturized and have improved patient mobility, easy of wearability, and routinely allow discharge from the hospital. Portable pneumatic drivers and battery packs are compact and lightweight and can be worn on a shoulder strap or towed on a luggage-type carrier. Most patients can achieve New York Heart Association functional status I or II while supported on a VAD. Patients can also achieve significant gains in physical and physiologic rehabilitation and rebuild muscle mass, potentially stabilizing their cardiac condition [45]. Many patients can engage in light to moderate physical activity (including walking, driving, dancing, and even work).

Despite improvements in quality of life, mobility, and functioning for VAD patients, however, psychologic and cognitive problems are not uncommon. In the first 1 to 2 weeks postimplant while patients are often in the ICU they report coping well with the VAD and having low symptoms of distress but feel as if they were not doing as well as they had anticipated before VAD implantation [46]. Adjusting to the VAD can be psychologically difficult. Incorporating the machinery into their body can evoke feelings of a damaged body image and sense of self and these feelings can be especially traumatic if the VAD implantation is in response to an emergency [47]. Patients can feel vulnerable, apprehensive with the machinery sounds and alarms, and can fear a VAD malfunction [47]. Although patients may be too ill before implantation, psychotherapy afterward to address these issues may ease the transition onto a VAD and help them prepare for eventual transplant.

Although patients bridged to transplantation with a VAD have similar posttransplant physical recovery and emotional well-being as patients who never required VAD support, they may have poorer residual cognitive functioning posttransplant [16,48]. Cognitive impairments may in part be caused by the higher risk of thromboembolism while supported on a VAD. Although there is a low incidence of thromboembolic complications (0.24 per 100 LVAD days), a high incidence of circulating microemboli on transcranial Doppler ultrasonography has been demonstrated in VAD patients [49]. Using cognitive P300 evoked potentials as a general indicator of neurocognitive functioning, one study showed in the short term that VAD implantation could improve neurocognitive impairment by the time patients left the ICU [50]. Nevertheless, although many of the microembolic events are clinically silent [49] the chronic effect of microembolic events (ie, silent infarctions) on cognitive functioning is speculated to be significant over time. Although it is not feasible repeatedly to perform CT of the brain, transcranial Doppler may be beneficial for predicting the risk and periodic neuropsychologic or cognitive testing may identify silent cerebral infarctions [48].

Treatment issues: medications for psychiatric disorders

Although psychiatric symptoms may seem to be normal reactions to significant stresses of the transplant experience, lack of timely diagnosis and treatment can lead to unneeded suffering, reduced adherence to medical care, heightened physical pain, and greater functional impairment. Nevertheless, it is a complex challenge to identify and correct underlying pathophysiologic processes first that could be causing or contributing to psychiatric symptoms. There may be significant overlap in the physical and psychologic symptoms of the patient's medical condition and their psychiatric illness (see Box 3). If medications are needed to treat psychiatric symptoms, careful consideration must be given to the choice of medication, symptoms to be treated, side effects of the medications, adverse drug interactions, and the type and severity of organ failure with respect to alteration in pharmacokinetics. A full discussion of this topic is beyond the scope of this article (Table 2 provides some guidelines and suggestions). In these cases psychiatric consultation can assist in the diagnosis and selection and monitoring of psychotropics. Brief psychotherapy, even in the ICU setting, may also be beneficial.

In cases of delirium and other psychotic symptoms it is important to avoid medications that may worsen symptoms. Low doses of typical and atypical antipsychotics may be most appropriate in these circumstances. Haloperidol, risperidone, and quetiapine are common choices, depending on the route of administration available [51]. Haloperidol may be given parenterally or orally. The lowest possible doses of this medication are suggested because it may cause extrapyramidal (parkinsonian) symptoms;

akathisia; and neuroleptic malignant syndrome. Short-acting risperidone and quetiapine are currently only available in oral forms. Risperidone and olanzepine are available in a quick-dissolving tablet that dissolves in seconds when placed on the tongue and may be useful if swallowing pills is a problem. These medications still need to be swallowed after dissolution and require an intact gastrointestinal tract for absorption. Atypical antipsychotics can cause or worsen hyperglycemia and hyperlipidemia (which can also be side effects of immunosuppressive medications) and they also carry a small risk of QT prolongation [51]. When treating delirium regular scheduled doses of medication are preferable to as-needed doses to stabilize symptoms. Delaying treatment until symptoms become problematic and then using as-needed dosing may create a situation in which higher doses are needed to control behaviors.

Lithium and divalproex (sodium valproate, valproic acid) are commonly used to treat mania, but are complicated to use in the peritransplant period. Large fluid volume shifts, the combined nephrotoxicity of other medications, and frequent use of diuretics make use of lithium potentially dangerous and impractical. Divalproex has many drug interactions and also a small risk of hepatotoxicity. Its use in patients with liver disease is not recommended. Side effects of divalproex include thrombocytopenia, nausea, vomiting, and ataxia. Atypical antipsychotics can effectively treat symptoms of mania, psychosis, and mood dysregulation in these patients.

Anxiety symptoms may be safely treated short-term with benzodiazepines; however, use of these medications may cause or worsen symptoms of delirium and cognitive impairment. If a benzodiazepine is used, a short-acting medication with no active metabolites is suggested, such as lorazepam. The lowest possible dose for the shortest period of time is suggested. As with delirium, treating anxiety with a regularly scheduled medication, rather than as-needed, may allow more consistent alleviation of symptoms and avoid an escalation of symptoms or a requirement for a higher dose. For those patients with pre-existing alcohol or benzodiazepine addiction, care must be taken with longer-term use of benzodiazepines to avoid precipitating a relapse of the addiction. In general, although benzodiazepines are quick acting and effective for immediate treatment of anxiety, for patients with more persisting anxiety consideration of a nonaddicting agent for longer-term use is suggested.

Both anxiety and depression may be treated with selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, sertraline, and citalopram). These medications are relatively safe in the medically ill patient; however, it is important to be aware that fluoxetine has a relatively long half-life and that fluoxetine, paroxetine, and sertraline may have cytochrome P-450 drug-drug interactions with medications typically administered to these patients. Venlafaxine has relatively few drug-drug interactions but in high doses may worsen hypertension. Fluvoxamine and nefazodone have very significant interactions with calcinurein inhibitors and should

Table 2
Psychotropic medications in transplant patients

Medication	Most common uses in transplant	Issues
Antidepressants		
SSRIs	Depression/anxiety disorders[a,b]	
Fluoxetine		Long half-life, takes many days to clear after discontinuation; potential drug interactions
Paroxetine		Mild anticholinergic effects; discontinuation syndrome more problematic than other SSRIs; potential drug interactions
Sertraline		Potential drug interactions
Fluvoxamine		Raises levels of cyclosporine and tacrolimus by inhibition CYP450 3A4
Citalopram		Few drug interactions
Escitalopram		Few drug interactions
Tricyclics	Depression/anxiety disorders[b]	All have cardiac effects: cardiac conduction changes, tachycardia and arrhythmias have been described; QT prolongation
Amitriptyline		Significant anticholinergic side effects
Imipramine		Significant anticholinergic side effects
Nortriptyline		Fewer anticholinergic side effects; therapeutic level established (50–150 ng/mL)
Doxepin		Moderate anticholinergic side effects
Desipramine		Fewer anticholinergic side effects; may cause anxiety and agitation
Others		
Trazodone	Sleep	Risk of priapism; poor antidepressant efficacy, may help with medication-induced sleep disturbances and nightmares caused by PTSD
Mirtazapine	Depression/anxiety disorders	Increased appetite or weight gain, can reduce nausea, may cause neutropenia
Nefazodone	Depression	Potential severe hepatotoxicity; avoid in liver disease; raises levels of cyclosporine and tacrolimus by inhibition of CYP450 3A4
Bupropion	Depression/smoking cessation	Risk of seizure in high doses; dose reduction in hepatic failure
Venlafaxine	Depression/anxiety disorders/pain	Dose reductions in hepatic and renal failure; dose-dependent elevations in blood pressure
Duloxetine	Depression/pain	Potential hepatoxicity; avoid in end-stage renal disease and patients with hepatic dysfunction
Benzodiazepines		All have abuse potential; risk of withdrawal syndrome with abrupt discontinuation after continued use

Lorazepam	Anxiety disorders/alcohol and drug withdrawal[c]	No active metabolites; may be given orally, intramuscularly, intravenously
Diazepam	Anxiety disorders/alcohol and drug withdrawal	Long half-life; active metabolites
Clonazepam	Anxiety disorders	
Temazepam	Sleep	No active metabolites
Alprazolam	Anxiety disorders	Short half-life; risk of withdrawal between doses
Antipsychotics	Delirium/hallucinations/delusions[b]	
Typical		
Haloperidol		Use lowest possible dose; risk of extrapyramidal symptoms and neuroleptic malignant syndrome is less with intravenous administration
Atypical		
Risperidone	Delirium/hallucinations/delusions[b]	Risk of metabolic syndrome in all
Olanzapine		Similar to haloperidol in dose >6 mg Risk of metabolic syndrome, hyperlipidemia, hyperglycemia, weight gain
Aripiprazole		Less risk of metabolic syndrome
Ziprasidone		Less risk of metabolic syndrome; risk of QT prolongation
Quetiapine		Moderate risk of metabolic syndrome; some weight gain
Stimulants	Depression/fatigue/ADHD[b]	All have abuse potential; should see response within several days; may decrease appetite
Methylphenidate		Avoid in agitated depression
Dextroamphetamine		Small risk of cardiac side effects
Other medications		
Lithium	Bipolar disorder	Potential nephrotoxicity; serious side effects with toxic levels; drug interactions with diuretics, ACE inhibitors and others
Clonidine	Posttraumatic stress disorder	Risk of hypotension, sedation
Prazosin	Posttraumatic stress disorder	May help nightmares and sleep disturbance related to PTSD
Buspirone	Anxiety disorders	May have respiratory stimulating properties

Abbreviations: ACE, angiotensin-converting enzyme; ADHD, attention deficit–hyperactivity disorder; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitors.

[a] Anxiety disorders include the following: anxiety disorder secondary to medications and medical conditions, generalized anxiety disorder, posttraumatic stress disorder, phobias including social phobia, panic disorder, obsessive-compulsive disorder, and other anxiety disorders.

[b] These uses pertain to all drugs in the class.

[c] May be used to treat alcohol withdrawal, sedative-hypnotic withdrawal, and as adjunctive medication in other withdrawal states.

be avoided [52]. Bupropion may increase the risk for seizures at higher doses and can cause symptoms of restlessness or tremulousness. It should be used cautiously during the immediate peritransplant period until the patient is stable.

Neuropsychiatric side effects of immunosuppressive medications

Calcineurin-inhibiting immunosuppressive medications (tacrolimus and cyclosporine)

Calcineurin-inhibiting immunosuppressive medications (CIIs) are the mainstay of immunosuppressive medication regimens for most solid organ transplant recipients. Tacrolimus and cyclosporine seem to have similar neurotoxic side effect profiles with up to 40% to 60% of transplant recipients experiencing mild symptoms including tremulousness, headache, restlessness, insomnia, vivid dreams, photophobia, hyperesthesias and dysasthesias, anxiety, and agitation [53]. Moderate to severe neuropsychiatric side effects (ie, cognitive impairment, coma, seizures, focal neurologic deficits, dysarthria, cortical blindness, and delirium) occur less often but can reach 21% to 32% in the early postoperative period [53]. Although there can be many possible etiologies for neuropsychiatric symptoms or mental status in the early posttransplant period (see Boxes 5 and 6), the possibility that they reflect CII side effects should always be entertained.

The etiology of CII neurotoxicity is unclear, most likely multifactorial, and may involve biochemical or physiologic derangements or direct or indirect neurotoxic processes (eg, immune system dysregulation). CII neurotoxicity has been associated with biochemical and electrolyte derangements including higher plasma levels, intravenous administration, hypocholesterolemia, and hypomagnesemia [53]. Disruption of the blood-brain barrier, whether structural (eg, previous strokes, hypertension, ischemia-reperfusion injury) or physiologic (eg, HE), has also been associated with neurotoxicity and is hypothesized to cause neurotoxicity by allowing higher CII drug levels in the CNS [53].

Correcting the metabolic disturbance or decreasing the drug blood level can result in a resolution of symptoms, although for severe symptoms the type of CII may need to be switched (eg, from tacrolimus to cyclosporine) or discontinued altogether. Anticonvulsants can successfully treat CII-induced seizures and are not required long-term. Seizures may cease if reduction or discontinuation of the drug is possible [53]. Treatment of mild symptoms can include sleep medications for sleep disruption or benzodiazepines or β-blockers (if the cardiovascular system can tolerate β blockade) for symptoms of anxiety, tremor, or restlessness. These treatments should be short-termed with the expectation that most symptoms caused by CII side effects spontaneously resolve as the CII blood levels are reduced

in the early posttransplant phase. The longer-term use of benzodiazepines is not recommend for symptoms of tremor, anxiety, or restlessness because the ability satisfactorily to taper patients off of these medications at a later point, especially after they develop physiologic and psychologic dependence, becomes problematic. The temporary use of these agents, however, may provide symptom relief as other antidepressants and anxiolytics are being instituted and adjusted to therapeutic doses. Serotonin reuptake inhibiting antidepressants can be more safely used long-term for symptoms of depression and anxiety, although these medications can take 3 to 4 weeks to become effective. Symptoms of cognitive impairment, agitation, and delirium can be treated with haloperidol or atypical antipsychotics. Psychiatric consultation is recommended to assist in the correct diagnosis and choice of appropriate medication therapy (see Table 2).

CIIs have also been associated with PRES. Clinical symptoms can be varied ranging from mental status changes to focal neurologic symptoms. Moderate to serious symptoms of neurotoxicity warrant a CT or MRI of the brain to evaluate for PRES (also seen in uremic encephalopathy). Characteristic neuroradiologic abnormalities (low attenuation of white matter on CT scan or corresponding hyperintense lesions on T2-weighted MRI images) are most commonly seen in the cortical and subcortical white matter typically involving the posterior lobes (parietal or occipital), although cases have been reported involving in the anterior brain, cerebellum, and brainstem [44]. Specific findings on MRI fluid attenuation inversion recovery sequences and apparent diffusion coefficient mapping (sensitive to water diffusion) provide further evidence toward the theory of neurotoxicity involving a vasogenic edema and may help compared with diffusion-weighted MRI images in distinguishing vasogenic from cytotoxic edema [54]. Although PRES usually occurs in the early postoperative period it can also occur years later. Both symptoms and radiologic findings can resolve with discontinuation of the CII.

Finally, a rare, severe multifocal demyelinating sensorimotor polyneuropathy has been seen in patients treated with CIIs and can occur within weeks posttransplant. Polyneuropathies in general can be severely limiting, may impair physical recovery, and could play a role in the liberation from mechanical ventilation. Early recognition of the symptoms is critical to recovery and sensitive electrophysiologic testing may be required. Many of these CII polyneuropathies can improve or be reversed following drug discontinuation, plasmapheresis, or intravenous immunoglobulin, suggesting an immune-mediated cause (eg, dysimmune neuropathy) [55,56].

Corticosteroids

Although chronic corticosteroid use is becoming less essential in transplant immunosuppression, high dosages are still used in the early postoperative

phase and also as "pulsed" dosages to treat acute rejection. Behavioral and psychiatric side effects of corticosteroids are well described but conclusions regarding the incidence, characteristic effects, or the specific dosages required to cause such effects are not well established. The reported incidence of serious psychiatric side effects is low (5%–6%) and includes a wide range of cognitive (diminished memory, concentration, attention, mental speed, distractibility), affective (depression, anxiety, irritability, emotional lability, hypomania, mania), psychotic (visual and auditory hallucinations, delusions, thought confusion, racing thoughts), and behavioral (restlessness, agitation, hypervigilance, aggression) symptoms [57–60]. Although dosage is not clearly related to timing, nature, intensity, or duration of symptoms [58], the risk of steroid psychosis mainly occurs with dosages of 40 mg/day or more of prednisone or its equivalent [59]. The average length of time from the institution of steroid therapy to the onset of steroid psychosis is 6 days [59]. Pre-existing personality disturbances, psychiatric disorders, or prior history of steroid psychosis does not clearly increase risk [57,59]. Brain wave slowing, including electroencephalographic increases in central theta activity [61] and decreases in amplitude and frequency of α-rhythm [59], can be seen and normalize following corticosteroid withdrawal.

Similar to the treatment of CII side effects, the treatment of steroid-induced symptoms should target specific symptoms with the expectation that therapy will only be required during steroid therapy. For most transplant patients steroids can be dramatically reduced or eliminated, which should alleviate the symptoms. The use of sleep medications or benzodiazepines may be effective short-term. Serotonin reuptake inhibiting antidepressants can be more safely used long-term for symptoms of depression, anxiety, or mood dysregulation but may require 3 to 4 weeks to become effective. The use of haloperidol or atypical antipsychotics can also be effective for mood dysregulation, psychosis, mania, irritability, agitation and aggression, or delirium. Psychiatric consultation is recommended to assist in the correct diagnosis and choice of appropriate medication therapy (see Table 2).

Special issues

Living donation

Living donors constitute 44% of all organ transplant donors in the United States [62]. Most living donors donate a kidney (95%) or a portion of the liver (4%). The remaining 1% consists of pancreas, intestine, and lung donors. Living donors may be related to the recipient biologically (eg, siblings) or emotionally (eg, spouses, close friends); or may have more distant relationships (eg, acquaintances through an organization, such as a faith-based group); or may have no relationship (ie, anonymous or altruistic donors).

Living donors constitute a unique patient population in that they are healthy individuals who receive a major surgical intervention solely for

the benefit of another person. Because it is critical to minimize both the psychologic and the physical risks for these individuals, they receive not only careful medical evaluations but careful psychosocial assessments to determine their suitability and willingness to donate. Even the healthiest donors, however, can have medical or psychiatric complications perioperatively or later in their recovery.

Before considering psychiatric sequelae in particular, it is noteworthy that the general medical outcomes of living donor surgery show an increasingly favorable profile, especially in kidney and liver donors [63–66]. The literature in other types of donors (eg, lung, intestine) is extremely sparse and the focus here is on kidney and liver donors. The perioperative mortality rate among kidney donors is 0.03% [64,65]. Several large patient series (numbers of 3000–5500) report that perioperative major complications (eg, re-exploration for bleeding) occur in less than 1% of donors [65]. Minor perioperative complications (eg, urinary tract infection, wound infection, need for blood transfusion) are more common, occurring in 4% to 8% of donors [65]. Although there are greater risks when donating a portion of the liver [63,67], the perioperative mortality rate for living liver donors is low (0.2%–0.3%) [63,66]. Recent patient series have shown overall rates of complications to be 14% to 32%, with the minor complication of biliary leakage being particularly prevalent [66]. Although the very long-term medical outcomes of liver donation are not yet known, the liver regenerates and the risk of long-term hepatic damage is believed to be low [66]. In kidney donation, the data available to date suggest low risk of renal disease or other organ system impairment even 20 to 30+ years postdonation [68]. Long-term follow-up data remain sparse, however, even for kidney donors.

Reported rates of perioperative psychiatric disturbances in living donors are quite variable, ranging from 0% to 14% [69–73]. These disturbances include delirium, anxiety, depression, and rarely psychosis. It should be noted that these rates are generally based on referrals for psychiatric evaluation and likely underestimate the actual numbers of donors experiencing psychiatric distress early in their recovery from surgery. Donors frequently comment that their perioperative pain was much greater than they had expected [74,75]. In addition, because of the perioperative steroids used to reduce inflammation, donors may experience restlessness, agitation, insomnia, and emotional lability. Because donors are healthy before donation, they may be more alert and less impaired postoperatively and can be more observant of the sights and sounds of the ICU environment, which can be emotionally disturbing. ICU staff should be attentive to donor psychic and physical discomfort. Donors should be asked about their emotional state and level of pain, and every effort should be made to alleviate pain and psychiatric symptoms or distress. Psychiatric or pain management consultation may be sought to ensure their comfort.

Despite these stresses most donors return to their former high levels of well-being following the initial recovery period after donation [76–78], and extremely few donors report that they regret having donated. They frequently report psychologic benefits from donation, including the gratification they experience in being able to help another person, and feelings of increased self-esteem [79–81].

Advanced directives: chronic rejection in lung transplantation as an example

The emphasis on aggressive if not sometimes heroic treatment of complications following transplantation is understandable given the general goal of medical care to protect and sustain life. This is especially relevant for transplant recipients because early identification and treatment may prevent worse complications or even loss of life. This goal of sustaining and extending life coupled with the tremendous commitment and effort put forth by the team, patient, and caregivers to get to and through transplant creates an environment in which dialogs about advanced directives are not often initiated [82].

Although this issue is important for all transplant patients, the development of chronic rejection in lung transplant recipients is a particular opportunity for such discussion. Chronic rejection of the lung transplant occurs in 60% to 75% of recipients by 5 years posttransplant and is the leading cause of death among recipients [82]. The clinical manifestation of chronic rejection is the bronchiolitis obliterans syndrome, and patients with this lesion have frequent hospitalizations often requiring mechanical ventilation in the ICU [83]. For lung transplant recipients, an ICU admission is associated with significant morbidity and mortality; only 43% are alive 1 year later and most die in the ICU [82,83].

Once chronic rejection is identified in lung recipients, the overall prognosis is poor but the course of illness can be highly variable. With these patients, as with other transplant recipients, the expected prognosis, their specific clinical course, and the risks of ongoing procedures, treatments, and interventions should be discussed with exploration of the patient's preferences. Optimally, these discussions should be undertaken when the situation is not dire, potentially when the patient is not ill or hospitalized. Unfortunately, these opportunities are often missed [82] and the ICU and transplant teams may need to consider discussions of palliative care and end-of-life decisions while the patient is critically ill.

Health care provider stress from repeated losses

Health care providers who care for patients awaiting transplantation inevitably experience the loss of some of these patients before a donor organ becomes available. Even posttransplant over the course of repeated hospitalizations or a prolonged stay, health care providers may become close to certain patients and emotionally invested in their outcome. The deaths of

these patients may be especially difficult to accept. With repeated experiences of caregiving and loss, health care providers may develop burnout caring for transplant patients. In turn, burnout leads to emotional exhaustion, feeling a lack of personal accomplishment, and negative attitudes toward patients, ultimately compromising caregiver effectiveness [84,85]. Avoiding burnout requires sensitivity to the impact of end-of-life issues and patient deaths on critical care staff. In addition, temporary reductions in clinical workload, greater attention to patient assignments, individual or group discussions after the loss of a patient, and added support from colleagues help to reduce burnout [4,86,87]. Novel approaches to burnout have incorporated additional techniques, such as the use of mindfulness meditation [88].

Summary

Transplantation is a challenging process for patients, caregivers, and medical professionals alike. Patients undergo acute and chronic pathophysiologic changes and can experience substantial emotional distress with the tremendous lifestyle changes and psychologic stresses they must endure. These stresses are accentuated in the ICU setting where the life-threatening nature of their medical state brings these issues to sharp focus. Although the ICU may be only one period of the patient's transplant hospital experience it is a critical time and the care provided by the ICU team is essential to their immediate and overall long-term outcomes. In addition to their medical needs the ICU staff must address the psychologic and psychiatric needs of the patients. Psychiatric disorders are common in these patients and their identification and prompt treatment are important aspects of the ICU teams care. This article reviews the essential aspects of the transplant process with specific relevance to the ICU stay. Psychiatric disorders common to transplantation are also described and discussed. This overview should provide ICU staff the information necessary to deal with the psychiatric needs of this unique and complex patient population.

References

[1] U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Available at: http://www.optn.org. Accessed December 1, 2007.

[2] 2006 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1996–2005. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD Retrieved online at: www.optn.org/AR2006/default.htm. Accessed December 1, 2007.

[3] Russo MW, Galanko JA, Shrestha R, et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl 2004;10:1018–23.

[4] Wright L, Pape D, Ross K, et al. Approaching end-of-life care in organ transplantation: the impact of transplant patients' death and dying. Prog Transplant 2007;17:57–62.

[5] Larson AM, Curtis JR. Integrating palliative care for liver transplant candidates: "too well for transplant, too sick for life. JAMA 2006;295:2168–76.

[6] Quill TE. Initiating end-of-life discussions with seriously ill patients: addressing the "elephant in the room". JAMA 2000;284:2502–7.
[7] Back AL, Arnold RM, Quill TE. Hope for the best, and prepare for the worst. Ann Intern Med 2003;138:439–43.
[8] Crone CC, Wise TN. Psychiatric issues in transplantation. II: Preoperative issues. Crit Care Nurse 1999;19:51–63.
[9] Trumper A, Appleby L. Psychiatric morbidity in patients undergoing heart, heart and lung, or lung transplantation. J Psychosom Res 2001;50:103–5.
[10] Parekh PI, Blumenthal JA, Babyak MA, et al. Psychiatric disorder and quality of life in patients awaiting lung transplantation. Chest 2003;124:1682–8.
[11] Rocca P, Cocuzza E, Rasetti R, et al. Predictors of psychiatric disorders in liver transplantation candidates: logistic regression models. Liver Transpl 2003;9(7):721–6.
[12] DiMartini AF, Dew MA, Trzepacz PT. Organ transplantation. In: Levenson JL, editor. The American psychiatric publishing textbook of psychosomatic medicine. Washington, DC: The American Psychiatric Press, Inc.; 2005. p. 675–700.
[13] Dew MA, DiMartini AF. Psychological disorders and distress after adult cardiothoracic transplantation. J Cardiovasc Nurs 2005;20(Suppl 5):S51–66.
[14] Olbrisch ME, Benedict SM, Ashe K, et al. Psychological assessment and care of organ transplant patients. J Consult Clin Psychol 2002;70:771–83.
[15] Skotzko CE, Strouse TB. Solid organ transplantation. In: Wise MG, Rundell JR, editors. The American psychiatric publishing textbook of consultation-liaison psychiatry: psychiatry in the medically ill. Washington, DC: The American Psychiatric Press, Inc.; 2002. p. 623–55.
[16] Dew MA, Kormos RL, Winowich S, et al. Quality of life outcomes after heart transplantation in individuals bridged to transplant with ventricular assist devices. J Heart Lung Transplant 2001;20(11):1199–212.
[17] Dobbels F, Verleden G, Dupont L, et al. To transplant or not? The importance of psychosocial and behavioural factors before lung transplantation. Chron Respir Dis 2006;3(1): 39–47.
[18] Levenson JL, Olbrisch ME. Psychosocial screening and selection of candidates for organ transplantation. In: Trzepacz P, DiMartini A, editors. The transplant patient: biological, psychiatric and ethical issues in organ transplantation. UK: Cambridge University Press; 2000. p. 21–41.
[19] Dew MA, Myaskovsky L, Switzer GE, et al. Profiles and predictors of the course of psychological distress across four years after heart transplantation. Psychol Med 2005;35: 1215–27.
[20] DeVito Dabbs A, Dew MA, Stilley CS, et al. Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation. J Heart Lung Transplant 2003;22(22):1268–75.
[21] Bunzel B, Laederach-Hoffman K. Solid organ transplantation: are there predictors for post-transplant noncompliance? A literature overview. Transplantation 2000;70:711–6.
[22] Trzepacz PT, Levenson JL, Tringali R. Psychopharmacology and neuropsychiatric syndromes in organ transplantation. Gen Hosp Psychiatry 1991;13:233–45.
[23] House R, Trzepacz PT, Thompson TL. Psychiatric consultation to organ transplant services. In: Tasman A, Goldfinger SM, Kaufman CA, editors. Review of psychiatry, vol. 9.Washington, DC: American Psychiatric Press; 1990. p 515–35.
[24] House RM, Thompson TL. Psychiatric aspects of organ transplantion. JAMA 1988;260(4): 535–9.
[25] Levenson JL, Olbrisch ME. Psychiatric aspects of heart transplantation. Psychosomatics 1993;34(2):114–23.
[26] Dew MA, Kormos RL, DiMartini AF, et al. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics 2001;42:300–12.

[27] Dew MA, Kormos RL, Roth LH, et al. Early post-transplant medical compliance and mental health predict physical morbidity and mortality 1-3 years after heart transplantation. J Heart Lung Transplant 1999;18:549–62.
[28] DiMartini A, Dew MA, Kormos R, et al. Post-traumatic stress disorder caused by hallucinations and delusions experienced while delirious. Psychosomatics 2007;48(5):436–9.
[29] Cuthbertson BH, Hull A, Strachan M, et al. Post-traumatic stress disorder after critical illness requiring general intensive care. Intensive Care Med 2004;30:450–5.
[30] Coffman K, Crone C. Rational guidelines for transplantation in patients with psychotic disorders. Current Opinions in Organ Transplantation 2002;7:385–8.
[31] Dew MA, Dimartini AF, Steel J, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver and other organs. Liver Transpl 2008;14:159–72.
[32] Liu LU, Schiano TD, Lau N, et al. Survival and risk of recidivism in methadone-dependent patients undergoing liver transplantation. Am J Transplant 2003;3:1273–7.
[33] Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med 2006;144:127–34.
[34] Tarter RE, Switala JA, Arria A, et al. Subclinical hepatic encephalopathy: comparison before and after orthotopic liver transplantation. Transplantation 1990;50:632–7.
[35] Parekh PI, Blumenthal JA, Babyak MA, et al. Gas exchange and exercise capacity affect neurocognitive performance in patients with lung disease. Psychosom Med 2005;67: 425–32.
[36] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium related stress in hospitalized patients with cancer, their spouses/caregivers and their nurses. Psychosomatics 2002;43(3):183–94.
[37] Bajaj JS, Saeian K, Verber MD, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. Am J Gastroenterol 2007;102:754–60.
[38] Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy: definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th world congresses of gastroenterology, Vienna, 1998. Hepatology 2002;35:716–21.
[39] David A, Sass A, Shakil O. Fulminant hepatic failure. Liver Transpl 2005;11(6):594–605.
[40] Stravitz RT, Kramer AH, Davern T, et al. Acute intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. Crit Care Med 2007;35:2498–508.
[41] Weissenborn K, Bokemeyer M, Krause J, et al. Neurological and neuropsychiatric syndromes associated with liver disease. AIDS 2005;19(Suppl 3):S93–8.
[42] Chung RT, Podolsky DK. Cirrhosis and its complications. In: Braunwald E, Fauci AS, Isselbacher KJ, et al, editors. Harrison's principles of internal medicine. 15th edition. New York: McGraw-Hill; 2001. p. 1754–66.
[43] Dejong CH, van de Poll MC, Soeters PB, et al. Aromatic amino acid metabolism during liver failure. J Nutr 2007;137:1579S–85S.
[44] Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2007;28:1320–7.
[45] McCarthy PM. Implantable left ventricular assist device bridge to transplantation: natural selection, or is this the natural selection? J Am Coll Cardiol. 2002;39:1255–7.
[46] Grady KL, Meyer P, Mattea A, et al. Improvement in quality of life outcomes 2 weeks after left ventricular assist device implantation. J Heart Lung Transplant. 2001;20:657–69.
[47] Chapman E, Parameshwar J, Jenkins D, et al. Psychosocial issues for patients with ventricular assist devices: a qualitative pilot study. Am J Crit Care. 2007;16(1):72–81.
[48] Komoda T, Drews T, Sakuraba S, et al. Executive cognitive dysfunction without stroke after long-term mechanical circulatory support. ASAIO J 2005;51:764–8.
[49] Thoennissen NH, Schneider M, Allroggen A, et al. High level of cerebral microembolization in patients supported with the DeBakey left ventricular assist device. J Thorac Cardiovasc Surg 2005;130:1159–66.

[50] Zimpfer D, Wieselthaler G, Czerny M, et al. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. ASAIO J 2006;52:24–7.
[51] Han C, Kim Y. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004;45(4):297–301.
[52] Fireman M, DiMartini AF, Armstrong SC, et al. Med-psych drug interactions update: immunosuppressants. Psychosomatics 2004;45(4):354–60.
[53] Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int. 2000;13(5):313–26.
[54] Ahn K, Lee JW, Hahn ST, et al. Diffusion-weighted MRI and ADC mapping in FK506 neurotoxicity. Br J Radiol 2003;76:916–9.
[55] Echaniz-Laguna Battaglia F, Ellero B, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in patients with liver transplantation. Muscle Nerve 2004;30:501–4.
[56] Wilson JR, Conwit RA, Eidelmann BH, et al. Sensorimotor neuropathy resembling CIDP in patients receiving FK506. Muscle Nerve 1994;17:528–32.
[57] Kershner P, Wang-Cheng R. Psychiatric side effects of steroid therapy. Psychosomatics 1989;30(2):135–9.
[58] Lewis DA, Smith RE. Steroid-induced psychiatric syndromes: a report of 14 cases and a review of the literature. J Affect Disord 1983;5(4):319–32.
[59] Hall RC, Popkin MK, Stickney SK, et al. Presentation of the steroid psychoses. J Nerv Ment Dis 1979;167(4):229–36.
[60] Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. Am J Psychiatry 1984;141(3):369–72.
[61] Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. Psychosom Med 1999;61:698–711.
[62] OPTN/UNOS Bylaws, Appendix B, attachment I, section XIII, C(2) and (4), designated transplant program criteria, programs performing living donor kidney and liver transplants approved, September 17, 2007. Available at: (www.unos.org);www.unos.org/news/newsdetail.asp?id-946. Accessed December 1, 2007.
[63] Middleton PF, Duffield M, Lynch SV, et al. Living donor liver transplantation: adult donor outcomes: a systematic review. Liver Transpl 2006;12(1):24–30.
[64] Matas AJ, Bartlett ST, Leichtman AB, et al. Morbidity and mortality after living kidney donation, 1999–2001: survey of United States transplant centers. Am J Transplant 2003; 3(7):830–4.
[65] Tan HP, Spector ZZ, Shapiro R. Perioperative donor risk [kidney]. In: Tan HP, Marcos A, Shapiro R, editors. Living donor transplantation. New York: Informa Healthcare; 2007. p. 69–79.
[66] Tan HP, Martin AE, Kilac A, et al. Donor outcomes [liver]. In: Tan HP, Marcos A, Shapiro R, editors. Living donor transplantation. New York: Informa Healthcare; 2007. p. 185–95.
[67] Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. N Engl J Med 2003;348:818–25.
[68] Davis CL. Long-term risks of living donation. In: Tan HP, Marcos A, Shapiro R, editors. Living donor transplantation. New York: Informa Healthcare; 2007. p. 77–85.
[69] Erim Y, Beckmann M, Valentin-Gamazo C, et al. Quality of life and psychiatric complications after adult living donor liver transplantation. Liver Transpl 2006;12:1782–90.
[70] Jacobs CL, Roman D, Garvey C, et al. Twenty-two nondirected kidney donors: an update on a single center's experience. Am J Transplant 2004;4:1110–6.
[71] Johnson EM, Remucal MJ, Gillingham KJ, et al. Complications and risks of living donor nephrectomy. Transplantation 1997;64:1124–8.
[72] Moss J, Lapointe-Rudow D, Renz JF, et al. Select utilization of obese donors in living donor liver transplantation: implications for the donor pool. Am J Transplant 2005;5:2974–81.
[73] Verbesey JE, Simpson MA, Pomposelli JJ, et al. Living donor adult liver transplantation: a longitudinal study of the donor's quality of life. Am J Transplant 2005;5:2770–7.

[74] Diaz GC, Renz JF, Mudge C, et al. Donor health assessment after living-donor liver transplantation. Ann Surg 2002;236:120–6.
[75] Kim-Schluger L, Florman SS, Schiano T, et al. Quality of life after lobectomy for adult liver transplantation. Transplantation 2002;73:1593–7.
[76] Bergman S, Feldman LS, Mayo NE, et al. Measuring surgical recovery: the study of laparoscopic live donor nephrectomy. Am J Transplant 2005;5:2489–95.
[77] Kok NF, Alwayn IP, Tran KT, et al. Psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy: a prospective study. Transplantation 2006;82:1291–7.
[78] Lumsdaine JA, Wray A, Power MJ, et al. Higher quality of life in living donor kidney transplantation: prospective cohort study. Transpl Int 2005;18:975–80.
[79] Clemens KK, Thiessen-Philbrook H, Parikh CR, et al. Psychosocial health of living kidney donors: a systematic review. Am J Transplant 2006;6(12):2965–77.
[80] Dew MA, Switzer GE, DiMartini AF, et al. Psychosocial aspects of living organ donation. In: Tan HP, Marcos A, Shapiro R, editors. Living donor organ transplantation. New York: Taylor and Francis; 2007. p. 7–26.
[81] Simmons RG, Klein SD, Simmons RL. Gift of life: the social and psychological impact of organ transplantation. New York: Wiley, 1977. Reprinted with additions, Brunswick, (NJ): Transaction Books, 1987.
[82] Song MK, De Vito Dabbs AJ. Advance care planning after lung transplantation: a case of missed opportunities. Prog Transplant. 2006;16(3):222–5.
[83] Hadjiliadis D, Steele MP, Govert JA, et al. Outcome of lung transplant patients admitted to the medical ICU. Chest 2004;125(3):1040–5.
[84] Poncet MC, Toullic P, Papazian L, et al. Burnout syndrome in critical care nursing staff. Am J Respir Crit Care Med 2007;175:698–704.
[85] Embriaco N, Papazian L, Kentish-Barnes N, et al. Burnout syndrome among critical care healthcare workers. Curr Opin Crit Care 2007;13:482–8.
[86] Levy MM. Caring for the caregiver. Crit Care Clin 2004;20:541–7.
[87] Espeland KE. Overcoming burnout: how to revitalize your career. J Contin Educ Nurs 2006; 37:178–84.
[88] Davies WR. Mindful meditation: healing burnout in critical care nursing. Holist Nurs Pract 2008;22:32–6.